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The Effect of Posterior Lobe Pituitary Gland Fractions on the Intact Human Uterus

BY

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THE clinical effects of undifferentiated extract of the posterior lobe of the pituitary gland are too well known to require elaboration. It is now generally agreed that at least two active principles can, in impure form, be obtained from the extract. One has the property of stimulating the plain muscle of the arteries and certain abdominal viscera; the other is exclusively concerned with the stimulation of the plain muscle of the uterus. The antidiuretic action of pituitary extract appears to be associated with the pressor fraction. It is still a moot point whether these principles exist in the body as separate entities, or whether they become such as the result of manipulation of the extract (Rosenfeld,[1] Du Vigneaud *et al*,[2] Van Dyke *et al.*[3]).

Separation of these principles was early attempted by H. W. Dudley,[4] whose chemical fractionation met with some success. Later, Kamm[5] and his co-workers elaborated a method of "salting-out" followed by chemical precipitations which has since become the basis of a commercial process. The vasopressor and oxytocic fractions are, in this country, generally known by the trade names of pitressin and pitocin given by the firm of Parke Davis and Company. Previously they were named vasopressin, and oxytocin respectively.

The dosage of posterior lobe pituitary extract is reckoned in "units," each of which represents the activity of a stated weight of standard posterior pituitary powder prepared and kept under specified conditions (Dale,[6]). "Units" of pressor activity refer to an action on the blood-pressure of the anaesthetized dog, while "units" of oxytocic activity refer to an action on the excised uterus of the virgin guinea-pig. The two units of measurement are therefore quite unrelated. In this country commercial preparations of the undifferentiated extract must by law conform to certain oxytocic standards. They are usually adjusted to contain 10 oxytocic units per cubic centimetre; the pressor activity of this quantity of extract varies between 5 and 10 units. In pitocin and pitressin a substantial separation of the two principles has been effected, but it should be noted that the differentiation is not complete, and each contains approximately 10 per cent of

the other reckoned in units of respective activity. Higher purification is possible, and special preparations have been used in many of the experiments to be described; but although these preparations are more specific, each still contains an appreciable content of the associated but unwanted fraction.

In the case of the oxytocic fraction (pitocin) it has generally been assumed that the effect seen in the isolated uterus of the test guinea-pig would be reproduced in the isolated or intact uterus of other mammals, including the human species. But this *a priori* reasoning is dangerous; there is the example of another endocrine extract, adrenaline, which also influences the uterus, but whose action, as is well known, varies qualitatively not only according to the species of animal tested but also according to the physiological state of the uterus at the time of test.

In the case of the vasopressor fraction (pitressin) it has generally been supposed that the physiological action is unrelated to uterine activity, and standardization has therefore been made with exclusive reference to the pressor effect on the dog. In this paper evidence is collected to show that this fraction does in fact also have an important stimulating effect on the human uterus, which, however, varies in degree according to the physiological state of that organ.

Doubt regarding the specificity of action of the two pituitary fractions seems first to have been raised by Robson.[7] Working with the excised uterus of the pregnant rabbit he showed that there were three stages of reactivity. During the first half of gestation neither fraction caused contraction; then followed a stage in which vasopressin caused a response but not oxytocin; lastly, as pregnancy advanced, oxytocin also caused contractions, the response becoming more and more powerful as parturition approached. In similar experiments on human uterine muscle (removed when operation on the pregnant uterus had become necessary) the second and third stages were identified, but material was not available before the 8th week when the first stage may have been present. Somewhat similar observations were made by Adair and Haugen;[8] in one case, that of an 8 weeks' gestation, they were unable to stimulate contractions by either pitocin or pitressin. Scott Russell,[9] working in this department, has corroborated certain of these findings and has carried the investigation further. He found that muscle strips removed from the lower uterine segment were much more responsive than similar strips from the upper segment. He further found that strips from the lower segment at term reacted 25 times more readily to pitressin than to pitocin. He suggested that such action as could be observed in the case of pitocin might well be explained by the residual content of pitressin.

Previous to these investigations, Bourne and Burn[10] had studied the behaviour of the intact human uterus during labour and had shown that intramuscular injection of oxytocin in doses as small as 2 units caused considerable increase in the magnitude and frequency of contractions; similar injection of 12½ units of vasopressin failed to produce any obvious response. In short, these workers found that the uterus in labour behaved in the manner of the excised non-pregnant uterus of the test guinea-pig. It will thus be seen that results almost directly opposed to each other have been obtained by workers using different methods of investigation.

Present Investigation.

Methods used.

My own experiments on the behaviour of the human uterus have been based on Bourne and Burn's work. These investiga-

tors used a small disc-shaped bag, of about 8 c.c. capacity. Mounted on a permanent wire-loop stilette, this bag was, with scrupulous regard to aseptic and antiseptic precautions, introduced between the uterine wall and the foetal membranes and passed above the presenting part of the foetus. It was then connected by water-filled tubing to a mercury manometer which, in turn, recorded the variations of intra-uterine pressure on a moving drum. I have used this method and extended it to serve for the following purposes: (1) It has been used as in Bourne and Burn's work to record the contractions of the uterus during labour. (2) After consultation with Professor F. J. Browne it was adapted for use in the puerperal uterus (Moir[11]). The wire stilette was bent to form an S-shaped curve; the bag could then be passed into the uterus and kept in position by a perineal band without discomfort to the patient. (3) Investigations were later extended to the non-pregnant uterus.[12] The bag used for this purpose was rather stout-walled, and had a capacity of between 1 and 2 c.c. of fluid; it was mounted on a thin metal tube shaped like a uterine sound, which served also as a stilette. (4) Sometimes pregnancy must, for medical reasons, be terminated in the early months: occasion is then provided for recording contractions. A bag of rather large size (about 5 c.c. capacity) was found convenient. It was inserted in the undisturbed uterus; or, alternatively, was inserted after the hysterotomy or other operation for evacuation of the uterus had been completed (Figs. 1 and 2).

An altogether different technique of uterine recording has also been employed for the pregnant and puerperal uterus. This makes use of a simplified form of the external abdominal tambour described by Dodek;[13] the apparatus is strapped to the abdomen and connected by water-filled tubing to a manometer and recording drum. Although not so reliable as the intra-uterine bag, the external apparatus can,

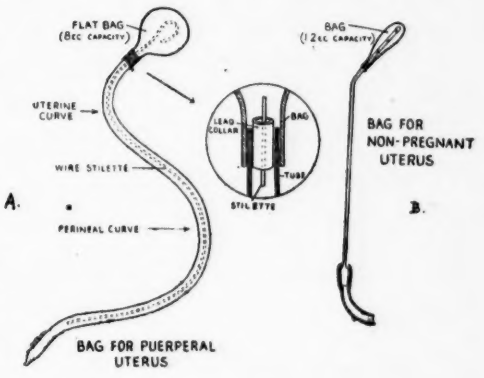

FIG. 1.

Bags used for (A) the puerperal, and (B) the non-pregnant uterus. After insertion, the bags are retained in position by tying to a waist-band.

on occasion, give surprisingly good results. My modification of Dodek's instrument has recently also been used to good purpose by Embrey.[14] (Fig. 3.)

THE NON-PREGNANT UTERUS.

The present investigation on the behaviour of the human non-pregnant uterus was started in 1933. At that time I had been concerned with the activity of the puerperal uterus—especially the response to ergot preparations—and it was natural to extend the investigation to the non-pregnant organ. This was done in the manner already described.

Examples of tracings are shown in Figs. 4 and 5. It will be noted that in the first half of the menstrual cycle the uterine contractions are irregular, small in magnitude, and come at intervals of 30 to 60 seconds. At about midcycle there is a gradual change; the small contractions disappear and are replaced by much larger and more prolonged contractions which come at intervals

of two to three minutes. I have been in the habit of calling these the A- and B-type waves respectively. The B-type waves become stronger, more regular, and usually more frequent as the cycle advances, and eventually merge with the contractions of menstruation. Fig. 4E shows the activity of the uterus at that time: incidentally, this tracing was, I believe, the first to be obtained showing the behaviour of the uterus during menstruation.

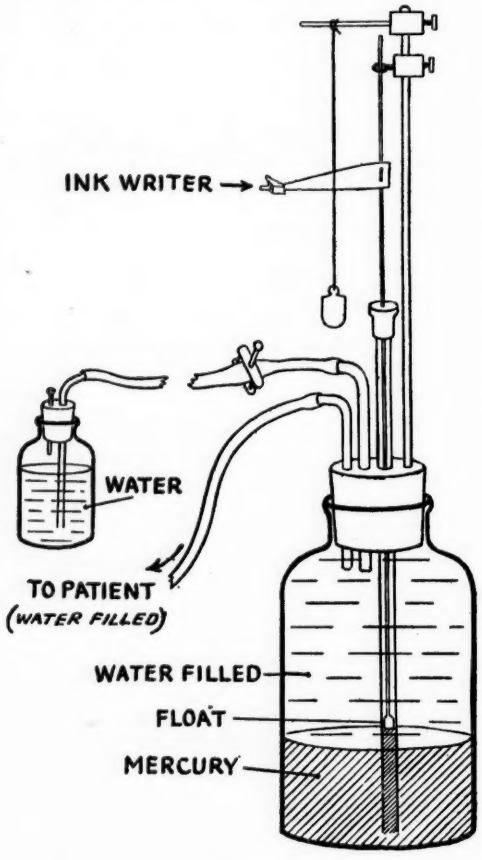

FIG. 2.

Mercury manometer, slightly modified from a design suggested by Sir H. H. Dale. At the beginning of the experiment the side bottle is raised to give any desired pressure in the recording system; the clamp is then closed. The time marker is omitted for the sake of clearness.

Response to undifferentiated pituitary posterior lobe extract.

Posterior pituitary extract was found to cause uterine contraction when given in a dose of 5 to 10 oxytocic units by intramuscular injection (Figs. 6 and 7). If given immediately before, during, or soon after menstruation the response was usually brisk; at other times the response tended to be rather slow of onset—a feature contrasting with the usual brisk effect of the drug on the uterus during labour or in the puerperium. This slower response was oftener seen in the second half of the menstrual cycle.

The response is almost constant. In only 4 out of more than 50 tests (half of which

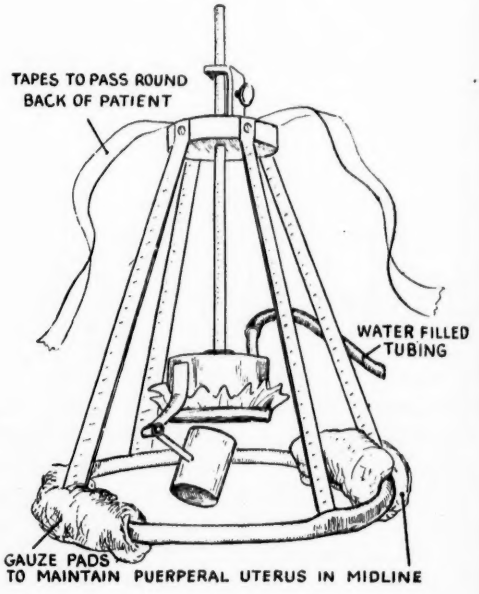

FIG. 3.

External apparatus (modified from Dodek) for the pregnant or puerperal uterus. During a contraction the uterus rears forward and pushes the cork against the tambour.

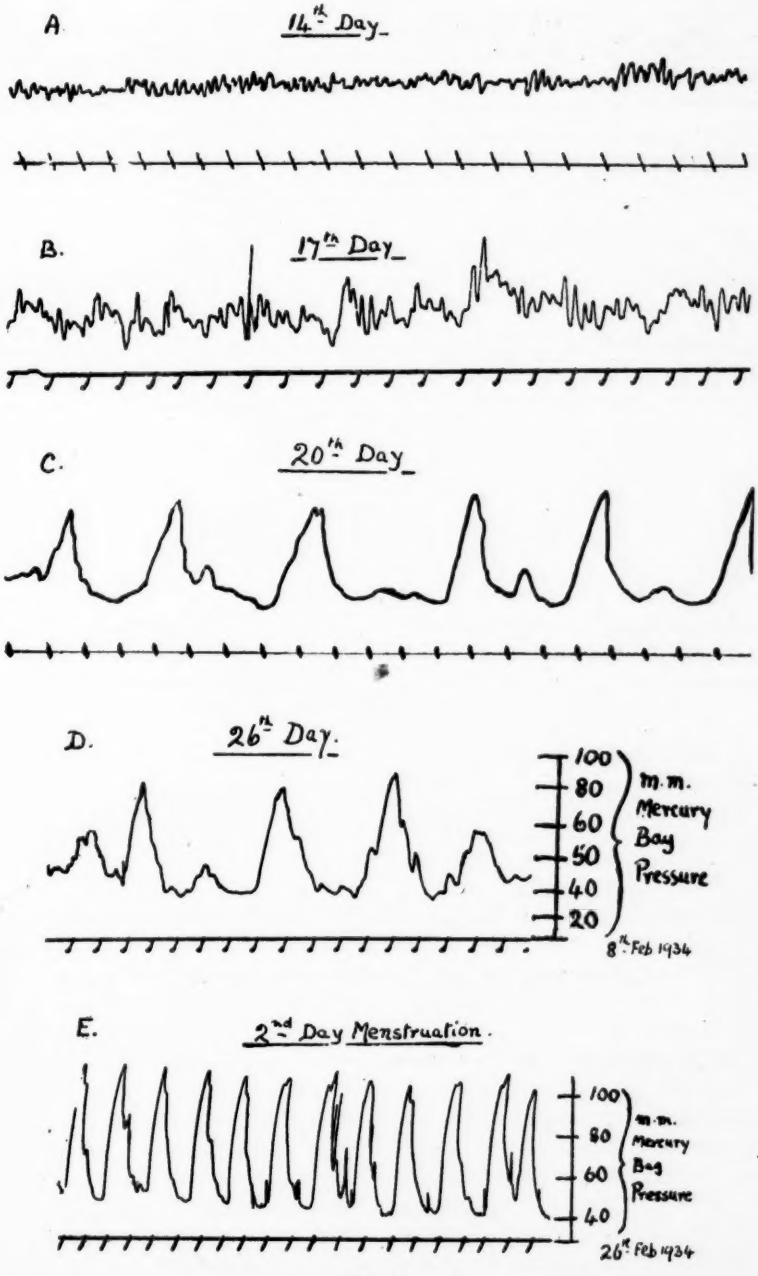

FIG. 4.

Uterine tracings obtained at various stages of the menstrual cycle (different women). A shows A-type contractions. B shows B-type contractions superimposed on A-type contractions. C and D show typical B-type contractions. E shows the contractions of menstruation. (Time marking in this, and in all subsequent tracings, is in minutes.)

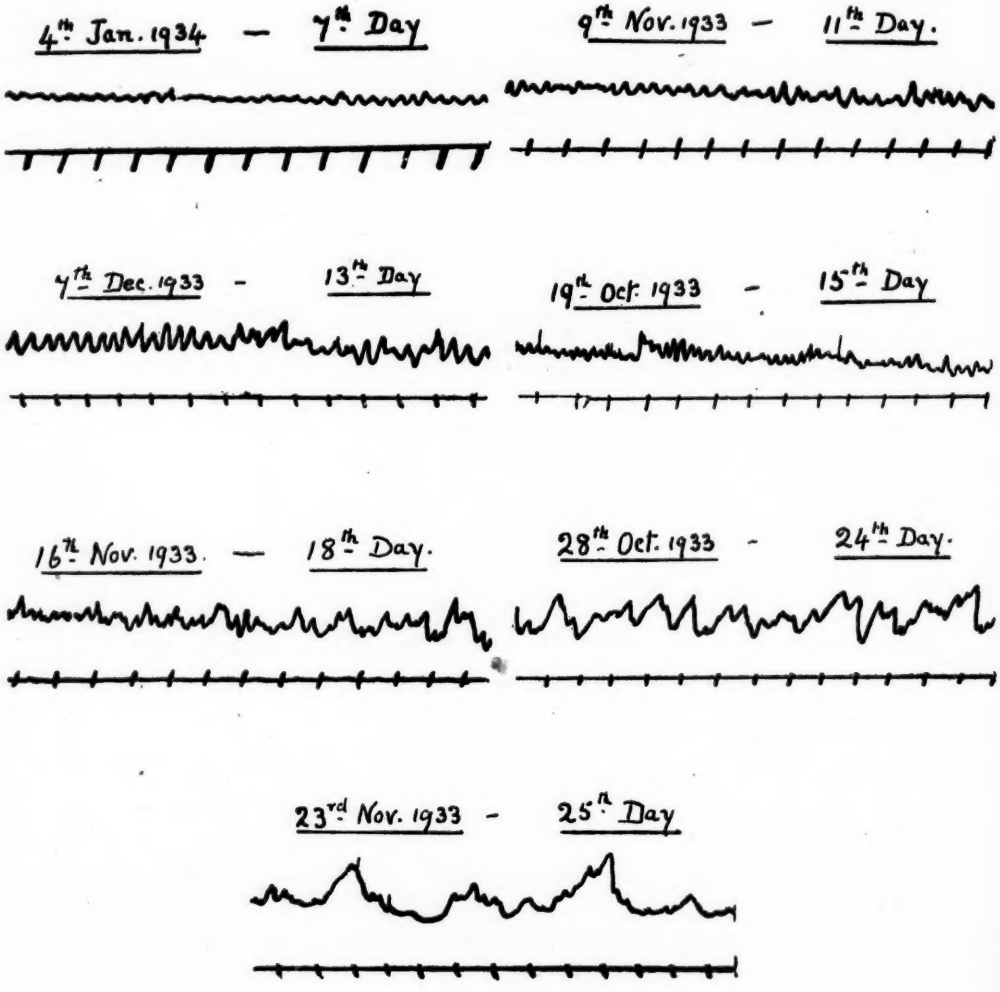
4th Jan. 1934 — 7th Day
9th Nov. 1933 — 11th Day.
7th Dec. 1933 — 13th Day
19th Oct. 1933 — 15th Day
16th Nov. 1933 — 18th Day.
28th Oct. 1933 — 24th Day.
23rd Nov. 1933 — 25th Day

FIG. 5.

Uterine tracings from one woman arranged according to stage of menstrual cycle.

were in the second stage of the cycle) has it been absent, and then neither spontaneous nor induced activity could be recorded. (The exceptions can probably be explained by a failure to insert the bag fully into the uterus, or to retain it in that position. In one case the uterus was unusually large and its motility may not have influenced the relatively small bag contained in its lumen.)

It may be said in criticism that all contractions recorded by this method are provoked or, at least, exaggerated by the irritation of the bag. This may be so, but two facts should be noted: the behaviour of the uterus alters quite consistently with

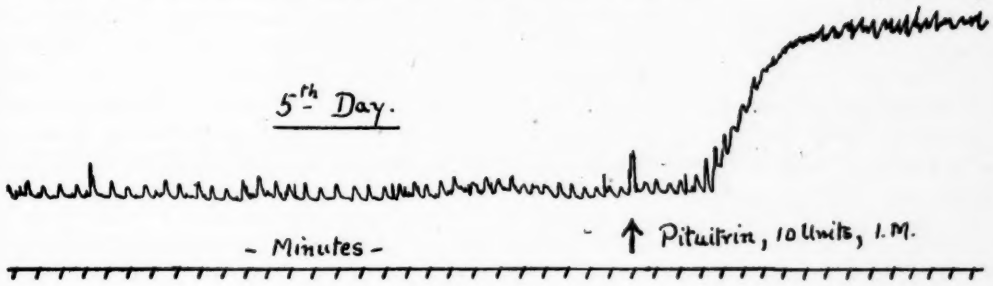

FIG. 6.

Tracing obtained 5 days after onset of menstruation and about 2 days after cessation of flow. There is still a " hang-over " of the B-type contractions. Brisk response to 10 units of posterior pituitary extract, by intramuscular injection.

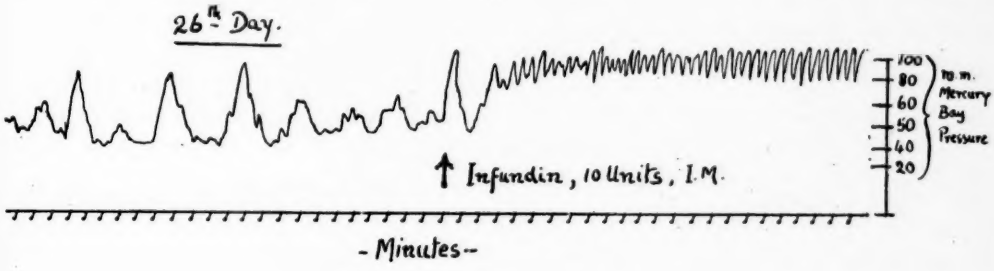

FIG. 7.

Twenty-sixth day of cycle. Brisk response to 10 units of posterior pituitary extract by intramuscular injection.

the stage of the menstrual cycle, and a response to posterior pituitary extract is present at every stage of the cycle.

Previously, Knaus[15] had described the behaviour of the non-pregnant uterus when that organ was injected with iodised oil as is done for radiological utero-salpingography. He stated that in the pre-ovulatory (follicular) phase the uterus was spontaneously active or could easily be roused to activity, whereas after mid-cycle, when the post-ovulatory (corpus-luteum) phase had started, it was inactive and unresponsive to posterior pituitary extract. These phases of ovarian activity have also been found to govern the behaviour of the rabbit uterus (Knaus,[16] Reynolds,[17, 18] Morgan[19]). Knaus further stated that in the human subject the sudden change of reactivity could be used as an indication of the time of ovulation. This work has been widely quoted in gynaecological literature, and the observations on ovulation from the basis of Knaus's law of periodic fertility and sterility in the human female.

The original method of recording in which oil was forced into the uterine cavity and allowed to leak slowly through the Fallopian tubes, had obvious disadvantages; it was not surprising, therefore, that at a later date it was discarded in favour of an intra-uterine balloon technique. In Knaus's hands this second method gave confirmatory results.[39]

Meanwhile, in my own work, observations were being made which, in certain

material respects were directly opposed to those of Knaus. While the pattern of contraction was found to vary with the stage of the menstrual cycle, activity was always present, and the uterus responded to posterior pituitary extract at every stage of the cycle including menstruation.[12] At first it was supposed that the subjects of these experiments might be women who showed a non-ovulatory type of menstrual cycle, that is, the uterus would not come periodically under the influence of a corpus luteum. (Here it may be noted that Knaus himself[20] has more recently also recorded examples in which the uterus continued to respond to pituitary extract throughout the menstrual cycle; he cites non-ovulatory menstruation as the cause for this allegedly abnormal response.) As more and more observations were made it became obvious that this simple explanation would not serve; a completely satisfactory explanation of the conflicting observations has, however, not yet come to light.

Since Knaus's early publications other investigators have studied this problem; some support Knaus's views, but others are at variance, and report findings that are in keeping with my own observations. Much of this literature has been reviewed by Klaften and Ruffel,[21] and by Kraul[22] and need not now be repeated. More recently, the work has been continued by various investigators in this country and in America. Robertson's[23] investigation is specially valuable. When recording the patterns of uterine motility he also secured small specimens of endometrium for biopsy, and was able to prove that a functioning corpus luteum could be present even in cases in which the uterus responded to pituitary extract. In eleven out of twelve cases pituitary extract caused uterine contractions in the second half of the menstrual cycle. Henry and Browne[40] made similar and fuller observations. Wilson and Kurzrok[24] also found that the uterus responded throughout the menstrual cycle. A similar investigation was made by McLellan[25] who again showed that in many cases the uterus continued to react to pituitary extract throughout the cycle; unfortunately he did not give details of the cases in which contractions were not recorded. Other contributions to this subject have been made by Bickers[26] and by Lackner, Wachtel and Soskin;[27] the latter workers found that the activity of the uterus and its response to pituitary extract varied so much in different individuals that its behaviour was in their opinion unpredictable.*

Bearing in mind the conflicting reports of different workers, it must be conceded that the behaviour of the human uterus recorded by the intra-uterine bag technique is influenced by the experimental con-

* In my early experiments the intra-uterine bag was stout-walled and contained, when fully dilated, about 3.2 c.c. of fluid; later a still smaller bag was used which contained less than 2 c.c. of fluid. In use, a balance of pressure was created with the wall of the balloon and adjacent uterine wall on the one side, and the recording column of mercury on the other. In this respect the method varied slightly from that of Knaus and some other investigators who have used thin rubber bags of large capacity which were intended to fill the entire uterine cavity, and which allowed the whole of the pressure of the recording fluid to be transmitted to the uterine wall. Reynolds[28] has reviewed the conflicting findings. He declares that a high recording pressure (60 mm. of mercury or more) will, in the corpus luteum stage of the cycle, when muscle is relatively lax, stimulate a spurious and artificial type of contraction. In my own work the intra-uterine bag was so small that this criticism is only doubtfully valid.[29] Further, in one case I modified my apparatus and reduced the fluid pressure to 10 mm. of mercury in conformity with Knaus's specification. A positive response to posterior pituitary extract in the second half of the menstrual cycle was still obtained: the patient menstruated 4 days later.

ditions of the test. It is, however, safe to say that the dogmatic statements originally made by Knaus cannot be upheld; in particular, his proposal that the change in reactivity to pituitrin should be adopted as a basis for determining the date of ovulation is unacceptable.

Response to the Pituitary Fractions.

Early in this work the pituitary fractions, pitocin and pitressin, were separately examined. At that time the results obtained came as a surprise. It was found that the uterus responded consistently to the pressor fraction (pitressin) but responded not at all to the oxytocic fraction (pitocin) (Moir[12]). Specially purified preparations had been obtained from Messrs. Parke Davis & Co., and, in view of the unexpected findings, Dr. Stanley White of that firm kindly arranged for the remainder of the solutions to be re-assayed. This was done, and the correctness of the original potency in oxytocic and vaso-pressor units was confirmed. Tests were later made with other samples, including commercial preparations of pitressin and pitocin. All subsequent experiments confirmed the original findings (Figs. 8 and 9). Study of the tracings strongly suggests that the activity of undifferentiated posterior pituitary extract on the non-pregnant uterus can be explained by the action of its pressor-factor content alone.

McLellan[23] published excellent tracings showing the effect of pituitary fractions on the non-pregnant uterus. As the result of careful quantitative tests he independently reached the conclusion that the human uterus in the non-pregnant state is " caused

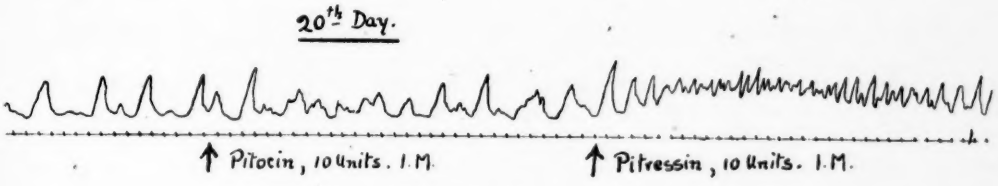

FIG. 8.

Twentieth day of cycle, showing response to pitocin 10 units, and pitressin 10 units, by intramuscular injection.

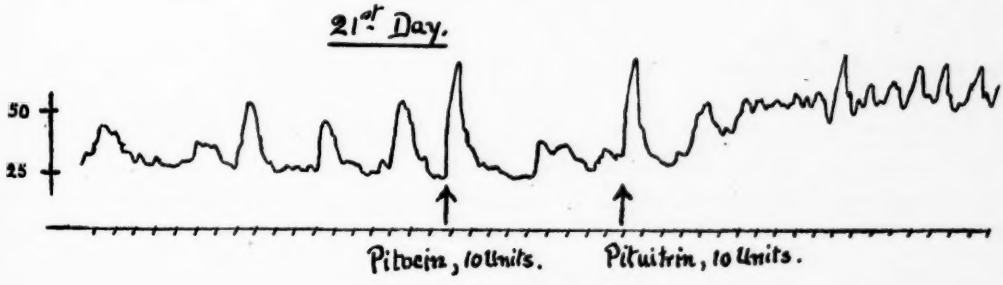

FIG. 9.

Twenty-first day of cycle, showing effect of pitocin 10 units, and pituitrin (undifferentiated posterior pituitary extract) 10 units, by intramuscular injection. (Similar results have been obtained in the first half of the menstrual cycle. Reversing the order of administration does not alter the effect of the extracts.)

to contract by vassopressin but not at all by oxytocin."

THE PREGNANT UTERUS.

(a) *Early Pregnancy.*

By selecting patients in whom pregnancy, for medical reasons, had to be terminated, recordings have been made by the intra-uterine bag method at the following stages of gestation (counting from the first day of the last menstrual period): 8 weeks, 9 weeks, 14 weeks, 16 weeks, 20 weeks, 22 weeks. In one case (14 weeks pregnancy) the experiment was made under cyclo-propane-nitrous oxide-oxygen anaesthesia; no uterine activity or reactivity could be detected. In each of the other cases the recordings were made on the conscious patient, and contractions were then always evident. As might be expected, the activity was comparatively feeble in the case of the undisturbed uterus; pituitary extract was then also relatively weak in action. When, however, recordings were made after operation for evacuation of the uterus, activity was much more evident, although contractions were usually irregular both in time and force. Posterior pituitary extract caused a considerably greater response from the organ in this irritable condition.

Specially interesting is Fig. 10. The first tracing showed the uterus almost inactive and only slightly responsive. The bag was then allowed to remain *in situ* for 24 hours, by which time the uterus was obviously in the process of aborting its contents. Records were again started. It will be seen that the uterus was now far more responsive to pituitary extract. Similar observations were made in another case.

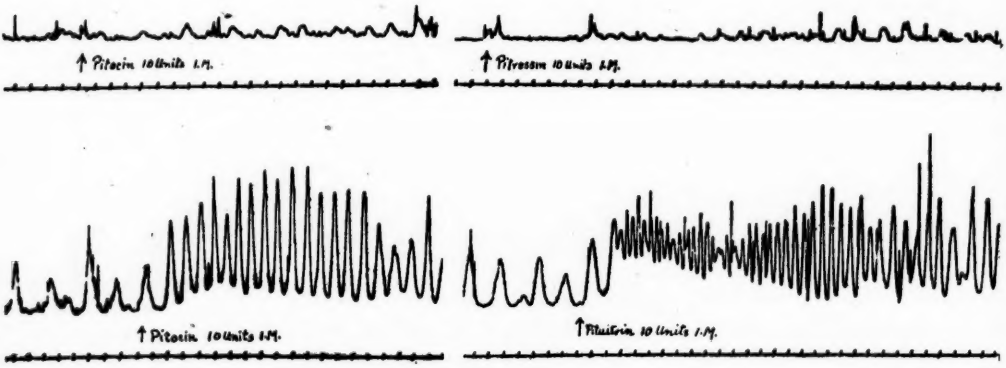

FIG. 10.

Contractions of the uterus during pregnancy, 13 weeks after 1st day of last menstrual period. Upper tracings made soon after insertion of bag. Pitocin 10 units, and pitressin 10 units administered by intramuscular injection. There is an interval of 17 minutes between the tracings. The lower tracings were obtained 24 hours later when the uterus was in process of aborting its contents. Pitocin 10 units, and pituitrin 10 units administered by intramuscular injection. There is an interval of 50 minutes between the tracings.

In each of the recordings in early pregnancy the uterus responded to pitressin in doses of 5 units intramuscularly, or 1 unit intravenously; it also responded to pitocin given in like doses of oxytocic units, but the response was not so brisk (Figs. 11 and 12). There were two possible exceptions. In one (9 weeks after last menstruation) pitocin in the excessive dose of 5 units intravenously was followed by pronounced uterine spasm. The other was the case

shown in Fig. 10 already described. Here the uterus, already stimulated to activity, showed an excellent response to pitocin; nevertheless, it will also be seen that a still greater response was evoked by the subsequent injection of undifferentiated extract, which, although equal in activity reckoned in oxytocic units, contained in addition the pressor factor of the posterior pituitary lobe.

Adair and Davis[30] also recorded the contractions of the intact human uterus in a patient at the 16th week of pregnancy. They found that similar contractions were produced by intravenous injection of 1 minim of pitressin and by 7 minims of pitocin.

These observations, though few in number, suggest that the undisturbed uterus is less responsive to posterior pituitary extract in early pregnancy than at other times. If, however, the uterus is already irritated, as it is when abortion occurs, there is a brisk response. The pressor fraction (pitressin) has a more constant,

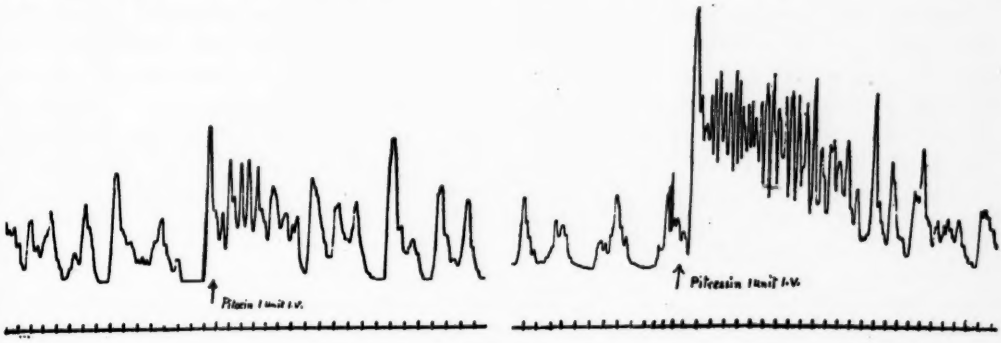

FIG. 11.

Tracing made after hysterotomy, 9 weeks after 1st day of last menstrual period. Pitocin 1 unit, and pitressin 1 unit, given by intravenous injection. There is an interval of 45 minutes between the two sections.

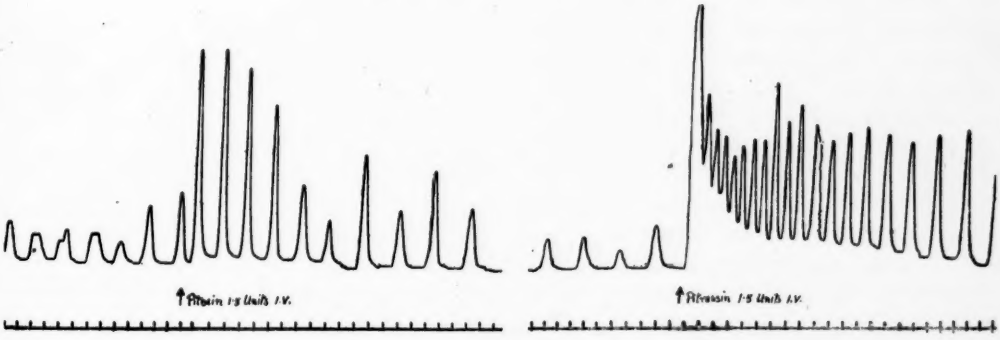

FIG. 12.

Tracing made after hysterotomy, 15 weeks and 2 days after 1st day of last menstrual period. Pitocin 1·5 units, and pitressin 1·5 units administered by intravenous injection. There is an interval of 5 minutes between the two sections.

and probably greater, effect than has the oxytocic fraction (pitocin).

It is also possible by direct methods to observe the effect of pituitary extract on the pregnant uterus. When the operation of abdominal hysterotomy is performed it is customary to inject pituitary extract into the uterine muscle a minute or two before opening the organ; blood loss is then greatly diminished. The intense uterine spasm so produced is easily observed by the blanching and the wrinkling of the uterine surface. When an early pregnancy has had to be terminated by this method, I have used the occasion to inject pitocin on one side of the uterus and pitressin on the other. Both extracts were found to cause a local spasm which soon spread throughout the organ; similar effects were not seen after injection of inert solutions. Although the test is too clumsy to allow any superiority to be ascribed to one or other preparation, it serves to confirm the experimental finding that both pitocin and pitressin have a motor effect on the pregnant human uterus.

(*b*) *Later months of Pregnancy.*

Many papers have been published on the muscular activity of the uterus at or near term. Some workers have used an external apparatus, notably the Lorand tocograph (Murphy[31]) or the Dodek recorder; others have employed an intra-uterine bag. The latter method has been much used for the reason that dilatation of the lower uterine segment is one of the standard methods of inducing labour. Bags used for this purpose are usually of the Vorhees or the De Ribes types, and are therefore much larger than required for simple recording of contractions. As already stated I have used the much smaller Bourne and Burn bag, which can easily be inserted above the presenting part of the foetus to lie between the membranes and the uterine wall. This bag is thick-walled, and when distended contains about 8 c.c. of fluid.

The tracings obtained in later pregnancy vary considerably from case to case. In some the uterus is seen to be relatively inactive, in others considerable activity is present, although the contractions are still painless in character. Sometimes the uterus has a high tone; sometimes it is relatively lax. These matters have been discussed elsewhere (Antoine,[32] Murphy[33,34]) and will not be further elaborated now.

Posterior pituitary extract in the relatively small dose of 2 oxytocic units by intramuscular injection, or a small fraction of 1 unit by intravenous injection has been found to cause a distinct increase in the force and frequency of the uterine contractions. The degree of effect depends on the previous condition of the uterus and is greater when spontaneous activity is already in evidence.

The posterior pituitary fractions have been separately tested on several occasions. In every trial both fractions stimulated uterine activity. But there was now a difference. Whereas pitressin was previously the more active when administered in the usual clinical dosage, matters were now reversed and pitocin caused contractions decidedly greater in magnitude than those caused by pitressin (Fig. 13).

(*c*) *Parturition.*

Since Schatz, 71 years ago, first used an intra-uterine bag to record contractions, many workers have studied the behaviour of the human uterus during labour. In recent times Bourne and Burn[35, 10] showed that a dose as small as 2 oxytocic units given by intramuscular injection substantially increased the strength and frequency of uterine contractions of a woman in labour. Their observations also led them to believe

that the substance responsible for the action on the human uterus resided exclusively in the so-called oxytocic fraction of the extract.

The uterine contractions of the 1st stage of labour are very similar to those of late pregnancy (Moir[36]). The response to undifferentiated pituitary extract is also similar although more pronounced. Unlike Bourne and Burn I have found that the uterus does respond to both fractions, although the response to pitressin is feeble compared with the spectacular response to pitocin (Fig. 14).

These experiments on the pregnant uterus clearly show that as gestation approaches term, the uterus changes in behaviour. Whereas in early pregnancy it reacts to pitressin, the response to that substance later somewhat declines; conversely the response to pitocin, previously uncertain, later becomes great, and as parturition approaches far surpasses the response to pitressin. The intact pregnant human uterus thus behaves towards these extracts in a manner similar to that of the excised uterus of the pregnant rabbit (Robson); and also—a circumstance both fortuitous and fortunate—it behaves at term similarly to the excised uterus of the

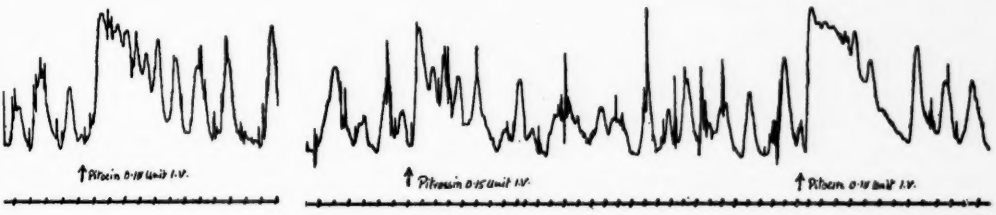

FIG. 13.

End of pregnancy, before onset of painful contractions. Pitocin 0.15 unit, pitressin 0.15 unit and pitocin 0.15 unit administered intravenously. An interval of 56 minutes separates the two sections.

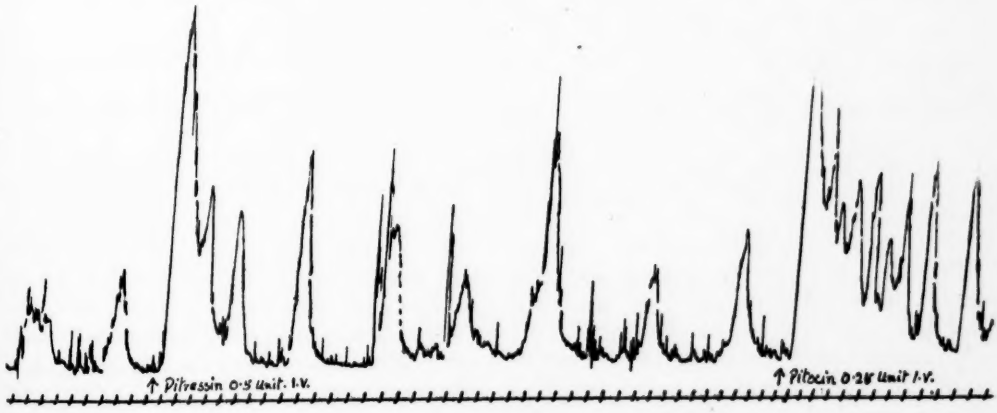

FIG. 14.

First-stage labour. Pitressin 0.5 unit, and pitocin 0.25 unit administered by intravenous injection.

non-pregnant guinea-pig, long accepted as the chief test object for pituitary extracts.

The Puerperal Uterus.

More than 160 recordings of the contractions of the puerperal uterus have been made with the intra-uterine bag method, and many more have been made with the external apparatus. While most of these experiments have been concerned with the response of the uterus to drugs other than those now under consideration, some 20 tests have been made with pituitary preparations.

The uterus after delivery normally contracts at regular and fairly frequent intervals—every 3 to 4 minutes. By the end of the first week the contractions come at longer intervals—10 minutes or more—and often there are long periods of relaxation. At this stage the uterus can be readily stimulated to activity; as example, the suckling reflex can usually be demonstrated (Fig. 15).

In the first few days of the puerperium the response of the uterus to pituitary extract is very similar to that seen in labour. After the first week the response becomes less marked, and, in a few cases, has failed to appear after the 8th or 9th day. Similar observations have been made by Bickers.[37] It is, however, necessary to add that as the puerperium advances it becomes increasingly difficult to introduce the standard bag in the uterus, and some failures of recording may have been caused by this fault. I have not investigated the behaviour of the uterus after the 10th day of the puerperium.

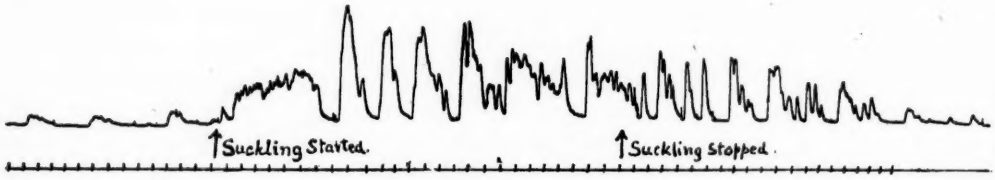

Fig. 15.
The effect of suckling on the puerperal uterus at the end of the first week.

Both pituitary fractions have been found to cause contractions of the puerperal uterus. During the first 3 or 4 days pitocin is decidedly more powerful than pitressin (Fig. 16). In the later puerperium my own observations are insufficient to assess the relative activity of the two fractions, although both are undoubtedly active (see later reference).

Adair and Davis[30] recorded uterine contractions by inserting a bag in the lower uterine segment after Caesarean section; later they extended the work to include the uterus in the puerperium. They found that the uterus responded readily to both pitressin and pitocin.

A careful quantitative investigation of the response of the puerperal uterus to pituitary fractions was made by Gardiner and Bradbury.[38] Using the intra-uterine bag technique they found that from the 6th to the 9th day of the puerperium the minimal effective dose of both pitressin* and pitocin was 0.01 c.c. (that is, 0.1 unit in the case of both the oxytocic and the pressor fractions). When the solutions were diluted to have an equal oxytocic activity on the non-pregnant uterus of

* Pitressin used contained 10 pressor units per c.c.; commercial pitressin contains 20 units per c.c.

the guinea-pig, the response of the human uterus was overwhelmingly in favour of pitressin. Proof is thus given that the activity of pitressin is not caused by contamination of pitocin. Pitressin is, in its own right, an oxytocic substance on the human uterus.

lobe pituitary gland extract also varies according to the physiological state of the uterus at the time of test.

3. Contrary to Knaus's observations, it has been found that the non-pregnant uterus responds to pituitary extract at every phase of the menstrual cycle, although

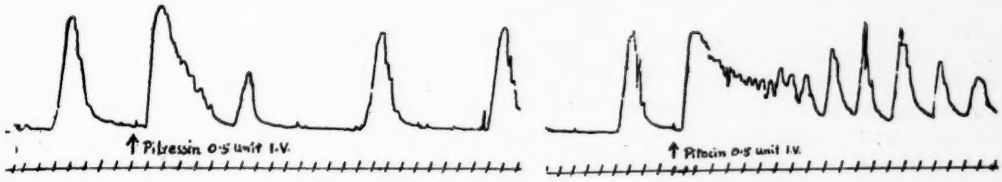

FIG. 16.

Third day puerperium. (Tracing made with external apparatus.) Pitressin 0.5 unit, and pitocin 0.5 unit administered by intravenous injection. There is an interval of 12 minutes between the two sections.

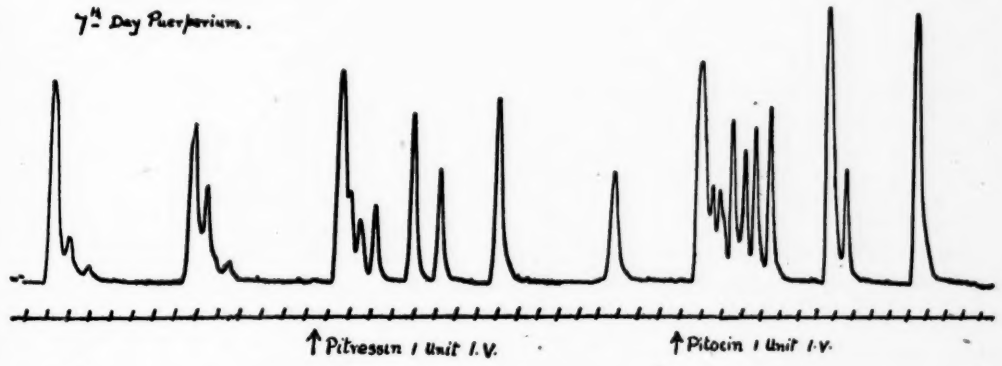

FIG. 17.

Tracing made on 7th day of puerperium by internal bag method. Pitressin 1 unit, followed by pitocin 1 unit, injected intravenously.

[NOTE: in this, as in previous tracings, the doses are stated in pressor and in oxytocic units respectively. In this case, if equal *volume* of pitressin had been given (that is, 2 pressor units) the effect of the two preparations would have been about equal. See text.]

CONCLUSIONS.

1. The muscular activity of the human uterus varies according to the physiological state of the organ. In the case of the non-pregnant uterus this is true also with regard to the phase of the menstrual cycle.

2. The response of the uterus to posterior response is most powerful immediately before, during, or soon after menstruation.

4. The response to pituitary extract during early pregnancy is weak, but it becomes strong if the uterus is already actively aborting its contents.

5. Given in the usual clinical dosage

the vaso-pressor fraction of the extract (pitressin) is sometimes a powerful stimulant of the uterus. Conversely, the oxytocic fraction (pitocin) is sometimes without action. The nature of the response to these fractions is governed by the physiological state of the uterus at the time of test. The changes are indicated in the accompanying table.

6. The response to pituitary extracts of an isolated muscle strip suspended in a saline bath does not necessarily reflect the behaviour of the intact uterus to these substances. In particular, an isolated strip of human uterus at term reacts in a substantially different manner towards pitocin and pitressin than does the intact human uterus. The cause of the anomalous behaviour is unknown.

TABLE I.

Summary of Action of Pitocin and Pitressin on the Intact Human Uterus.

	Pitocin	Pitressin
Non-pregnant	0	++
Early pregnancy (after 8th week)	very feeble	feeble
Ditto. Uterus already active	+	++
Late pregnancy (after 36th week)	++	+
Parturient	+++	+
Early puerperium	+++	+
6th to 9th day of puerperium	+	+

ACKNOWLEDGMENTS.

The work on the puerperal and non-pregnant uterus was chiefly done in the Obstetric Unit of University College Hospital, London, and was continued in the British Postgraduate Medical School (Hammersmith Hospital). In co-operation with Dr. A. K. Koff some observations were repeated in Johns Hopkins Hospital, Baltimore. Further work has been done in the Radcliffe Infirmary, Oxford. To the various hospital authorities concerned, to nurses, and particularly to Professor F. J. Browne and to Professor J. Young of the first two mentioned hospitals, I gladly express thanks for facilities and help generously given. Above all, to willing and tolerant patients I acknowledge deep debt, and express grateful though inadequate thanks.

REFERENCES.

1. Rosenfeld, M. *Bull. Johns Hopkins Hosp.*, 1940, lxvi, 398.
2. Irving, G. W. and V. Du Vigneaud. *Journ. Amer. Chem. Soc.*, 1940, lxii, 2080.
3. Van Dyke, H. B., B. F. Chow, R. O. Greep, and A. Rothen. *Journ. Pharmacol,* 1942, lxxiv, 190.
4. Dudley, H. W. *Journ. Pharmacol.*, 1923, xxi, 103.
5. Kamm, O., Aldrich, Grote, Rose, and Bugbee. *Journ. Amer. Chem. Soc.*, 1928, l, 573.
6. Dale, H. H. *Brit. Med. Journ.*, 1942, ii, 385.
7. Robson, J. M. *Journ. Physiol.*, 1933, lxxviii, 309: lxxix, 83.
8. Adair, F. L. and J. A. Haugen. *Amer. Journ. Obstet. and Gynecol.*, 1939, xxxvii, 753.
9. Russell, C. S., *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1943, l, 287.
10. Bourne, A. and J. H. Burn. *Lancet,* 1928, ii, 694.
11. Moir, C. *Brit. Med. Journ.*, 1932, i, 1022.
12. Moir, C. *Edinb. Med. Journ.*, 1934, xli, Trans. Edinb. Obstet. Soc., 93.
13. Dodek, S. M. *Surg., Gynecol. and Obstet.*, 1932, lv, 45.
14. Embrey, M. P. *Journ. Obstet. and Gynecol. Brit. Emp.*, 1940, xlvii, 371.
15. Knaus, H. *Zentrbl. Gynäkol.*, 1929, liii, 2193.
16. Knaus, H. *Arch. f. Gynäk.*, 1930, cxl, 181.
17. Reynolds, S. R. M. *Amer. Journ. Physiol.*, 1931, xcviii, 230.
18. Reynolds, S. R. M. and Allen, W. M. *Ibid,* 1932, cii, 39.
19. Morgan, T. N. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1935, xlii, 79.
20. Knaus, H. *Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes.* 1934, Vienna: Maudrich.

21. Klaften, E. and Z. Ruffel. *Zentrbl. Gynäk.*, 1935, lix, 2050.
22. Kraul, L. *Z. Geburtshülfe u. Gynäk.*, 1935, cxi, 273.
23. Robertson, E. M. *Edinb. Med. Journ.*, 1937, xliv, 20.
24. Wilson, L., and R. Kurzrok. *Endocrinology*, 1938, xxiii, 79.
25. McLellan, A. *Lancet*, 1940, i, 919.
26. Bickers, W. and R. J. Main. *Journ. Clin. Endocrinology*, 1941, i, 992.
27. Lackner, J. E., H. Wachtel, and S. Soskin. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxvi, 612.
28. Reynolds, S. R. M. *Physiology of the Uterus*, 1939. London: Hamilton.
29. Moir, C. *Lancet*, 1935, i, 53.
30. Adair, F. L. and M. E. Davis. *Amer. Journ. Obstet. and Gynecol.*, 1934, xxvii, 383.
31. Murphy, D. P. *Amer. Journ. Obstet. and Gynecol.*, 1940, xxxix, 808.
32. Antoine, T. *Physiologie und Pathologie der Wehen.*, 1935, Vienna: Maudrich.
33. Murphy, D. P. *Amer. Journ. Obstet. and Gynecol.*, 1941, xli, 274.
34. Murphy, D. P. *Surg. Gynecol. and Obstet.*, 1941, lxxiii, 175.
35. Bourne, A. and J. H. Burn. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1927, xxxiv, 249.
36. Moir, C. *Lancet*, 1936, i, 414.
37. Bickers, W. and R. J. Main. *Amer. Journ. Obstet. and Gynecol.*, 1942, xliv, 581.
38. Gardiner, S. and J. T. Bradbury. *Amer. Journ. Obstet. and Gynecol.*, 1940, xxxix, 1.
39. Knaus, H. *Zentralb. Gynäk.*, 1933, lvii, 2658.
40. Henry, J. S. and J. S. L. Browne. *Amer. Journ. Obstet. and Gynecol.*, 1943, xlv, 927.

The Anaemias of Pregnancy

A Report on the Haematological Study of 48 Cases of Pregnancy with a Review of the Literature.

BY

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Introduction.

It is important to distinguish between anaemia which is apparently due to pregnancy and anaemia which is associated coincidentally with pregnancy. In the present enquiry, the phrase "anaemia during pregnancy" denotes that a case is pregnant and anaemic at the same time. "Anaemia of pregnancy" and "pregnancy anaemia" are used synonymously to indicate that the anaemia is conditioned directly by pregnancy: it is perhaps too strong to refer to such anaemia as being due to pregnancy. "Anaemia complicated by pregnancy" indicates that pregnancy occurs coincidentally with some disorder of the blood which ordinarily occurs quite apart from and is quite unrelated to pregnancy.

Studies of anaemia occurring during pregnancy have been of two main types. The first type, from which information of great value has been collected, is the mass survey of large series of cases. Studies of such a nature have the disadvantage that the less common varieties of pregnancy anaemia are pooled among the more common. The second type of study, of which the present is an example, consists of a more detailed investigation of individual cases.

Present Investigation.

The object of the present investigation was to study in detail certain haematological characteristics in normal pregnancy and to compare these with the findings in anaemias of pregnancy. This necessitated a full haematological investigation in each case. From the findings the need for a reclassification of the anaemias of pregnancy became apparent, which in turn necessitated a review of the literature on the subject.

Clinical Material.

The patients examined were selected from the Antenatal Clinic and Obstetric Wards of Hammersmith Hospital. They were, with few exceptions, in poor circumstances, the diet being mainly carbohydrate. Many were visited in their homes, which were of semi-slum standard.

The total number of patients was 48. A patient was not included if there were any signs of toxaemia of pregnancy, pyelitis, heart disease or any other organic disease. Twenty of the 48 patients were selected as normal controls, the arbitrary "normal" decided upon at the outset of the investigation being that the patient should have a haemoglobin of 80 per cent Haldane or over, and should be free of all symptoms which could not be explained by a normal

* Dr. Elliott is serving with the South African Forces in the Middle East. This paper has been abridged for publication from his thesis for the degree of M.D. by Dr. Janet Vaughan.

pregnancy. It was recognized that this arbitrary standard of normality might have to be modified at a later date (see p. 208).

The following examinations were made on each patient when first seen, a red cell count, estimation of haemoglobin, mean corpuscular volume, reticulocyte percentage, plasma bilirubin, mean red cell diameter and median corpuscular fragility. In a number of patients the complete haematological investigation was repeated during pregnancy and again on one or more occasions postpartum. A history was taken and a clinical examination was also made.

Methods.

Red Cell Counts were made on capillary and heparinized venous blood within half an hour of the taking of the blood. An average of 4 counts was taken, 2 capillary and 2 venous. When venepuncture was not performed 2 counts on capillary blood were done.

White Cell Counts. A single count was made from either capillary or venous blood. The method employed was that described by Price-Jones, Vaughan and Goddard (1935).

Haemoglobin was measured by Haldane's method, using the same standard throughout. This standard agreed with the original standard used by Price-Jones, Vaughan and Goddard. It is realized that the comparison of haemoglobin estimations made by different methods is unsatisfactory, but until a standardized instrument is used all over the world there appears to be no alternative.

Mean Corpuscular Volume was estimated by Wintrobe's method (Wintrobe, 1930).

Plasma Bilirubin was estimated by the method of Haslewood and King (1937).

Mean Red Cell Diameter was estimated by the method of Price-Jones (1933).

Red Cell Fragility was determined by the method of Dacie and Vaughan (1938).

Results.

Normal Control Cases.

The results of haematological investigations in the 20 normal controls are summarized in Table I.

The haemoglobin percentage ranged between 80 and 100 per cent, the majority of the readings being nearer 80 than 100. The red cell counts ranged between 4.10 and 5.80 million per cu. mm. The colour index fell between 0.8 and 1.0, with one reading of 0.69. In how far a colour index of 0.8 can be regarded as being compatible with a normal blood picture will be considered after the facts of the colour index in the series have been presented. The mean corpuscular volume fell between the limits of 73 and 88 cu.μ with one exception of 62 cu. μ (a case with colour index of 0.69 and certain other unusual features to be discussed). The mean red cell diameter was measured on 14 cases and ranged between 6.7 and 7.7 μ. The accepted normal for males and non-pregnant females is 6.686 and 7.718 μ (Price-Jones 1933). The standard deviation varied between 0.466 and 0.708, the normal limits of Price-Jones (1933) and Mogensen (1938) being 0.430 to 0.535. The variability per cent ranged between 6.6 and 9.2 per cent, the upper limit of normal range being 7.3 per cent. The significance of this wide range, expressing as it does an abnormal degree of anisocytosis, will be discussed in a later section (p. 207). The results of the red cell fragility tests are tabulated in Table I and charted graphically in Figs. 1 and 2. It is seen that the composite curve of fragility for the 20 cases (Fig. 2) and the range of sodium chloride concentration within which the median corpuscular fragility lay (Fig. 1) extends to the left of the normal calculated limits indicated in this and subsequent graphs by the shaded area. It is of interest that in 11 instances the median corpuscular

TABLE I.

Haematological Study of 20 Normal Pregnancies.

Case	R.B.C.	Hb.%	C.I.	M.C.V.	V.P.C.	M.C.D.	M.C.T.	M.C.F.	V.	Sig.	Stage
1.	4.30	80	0.9	83	36			0.367			35
	4.11	79	1.0	85	35			0.350			3 dys. pp.
2.	4.66	90	1.0	82	38	7.6	1.8	0.393	8.8	0.667	30
12.	4.96	100	1.0	80	40	7.0	2.1	0.355	6.6	0.466	38
	4.83	84	0.9	85	41			0.348			7 wks. pp.
14.	5.40	82	0.8	76	41	7.2	1.9	0.350	8.9	0.637	39
	4.97	90	0.9	88	44			0.358			8 wks. pp.
16.	4.50	84	0.9	87	39	7.2	2.2	0.368	7.1	0.512	37
	4.58	90	1.0	90	41			0.349			4 dys. pp.
19.	4.80	80	0.8	73	35	7.1	1.9	0.393	7.6	0.533	38
23.	4.08	82	1.0	78	32	7.3	1.9	0.394	8.9	0.653	24
	3.90	76	0.9	87	34			0.384			32
25.	4.88	96	1.0	82	40	6.7	2.3	0.372	7.5	0.503	22
	4.09	80	1.0	88	36			0.380			30
35.	4.36	88	1.0	87	38			0.349			10
36.	5.80	80	0.7	62	36	6.8	1.7	0.388	7.5	0.510	38
38.	4.36	80	1.0	78	34	7.0	2.0	0.358	7.6	0.523	38
	4.71	88	0.8	91	43			0.356			12 wks. pp.
39.	4.68	82	0.9	83	39			0.348			20
44.	4.75	86	0.9	79	38	7.2	1.9	0.390	7.7	0.554	39
45.	5.30	88	0.9	88	47	6.7	2.5	0.374	7.9	0.524	37
46.	4.60	82	0.9	83	38			0.360			29
48.	5.10	84	0.8	77	40	7.3	1.8	0.366	8.5	0.626	39
51.	4.23	80	0.9	85	36	6.9	2.2	0.358	6.9	0.482	28
52.	4.91	82	0.8	76	37	7.7	1.6	0.348	9.2	0.708	39
	4.24	80	0.9	85	36			0.366			7 dys. pp.
55.	4.27	82	0.9	83	36			0.378			30
57.	4.10	80	1.0	88	36			0.380			30

Interpretation of abbreviations. R.B.C.—Red cell count in millions per cu.mm. Hb.%—Haemoglobin percentage (Haldane). C.I.—Colour Index. M.C.V.—Mean corpuscular volume. V.P.C.—Volume of packed red cells. M.C.D.—Mean red cell diameter. M.C.T.—Mean red cell thickness. M.C.F.—Median corpuscular fragility. V.—Variability per cent. Sig.—Standard deviation. Stage—Antepartum or postpartum period in weeks.

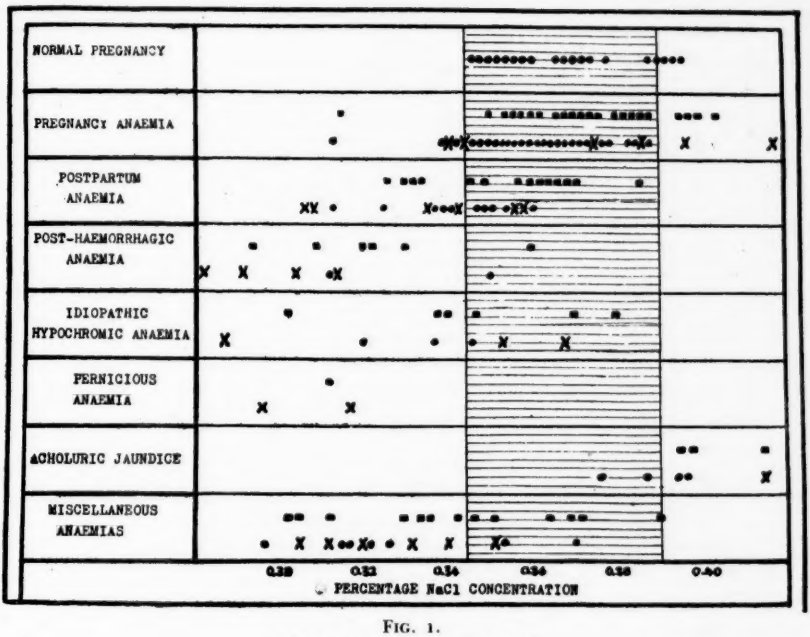

FIG. 1.

MEAN CORPUSCULAR FRAGILITY

in various types of anaemia. Shaded area indicates range of normal. Round dots indicate M.C.F. uncorrected, square dots indicate M.C.F. corrected for anaemia, crosses indicate cases with haemoglobin less than 50 per cent Haldane.

fragility (i.e. the concentration of sodium chloride at which 50 per cent of the cells are haemolysed) was greater than the observed normal limit but fell within the possible normal range calculated on a basis of $\pm 3\sigma$. Four of the 6 patients examined after delivery showed a postpartum decrease, a very common finding, as will be shown, in anaemia of pregnancy. Reticulocyte counts were made at stages varying from 28 to 37 weeks. With 3 exceptions the count was within normal limits, i.e. not above 2 per cent. Plasma bilirubin was estimated in 10 normal pregnancies and fell within normal limits (Vaughan and Haslewood 1938).

II. CASES OF ANAEMIA.

The results of the haematological investigations in the 28 anaemic patients are summarized in Table II.

The haemoglobin percentage of the 28 patients at the time of the first complete haematological investigation ranged from 32 to 76 per cent. The red cell counts ranged from 3.27 to 5.00 million per cu. mm. The mean corpuscular volume ranged between 58 and 98 cu. μ, 10 of the readings from the anaemia cases are below accepted normal levels and one (98 cu.μ) just above the upper level of normal for the non-pregnant state. The mean red cell diameter was measured in 10 cases and ranged from 6.0 to 7.4 μ, 4 out of 18 were below 6.76 μ, the lower limit of normal. The mean cell diameter tends to increase along with the colour index as treatment becomes effective. The standard deviation in the series varied from 0.495 to 0.911. The coefficient of variation (variability) varied from 6.8 to 13.3 per cent.

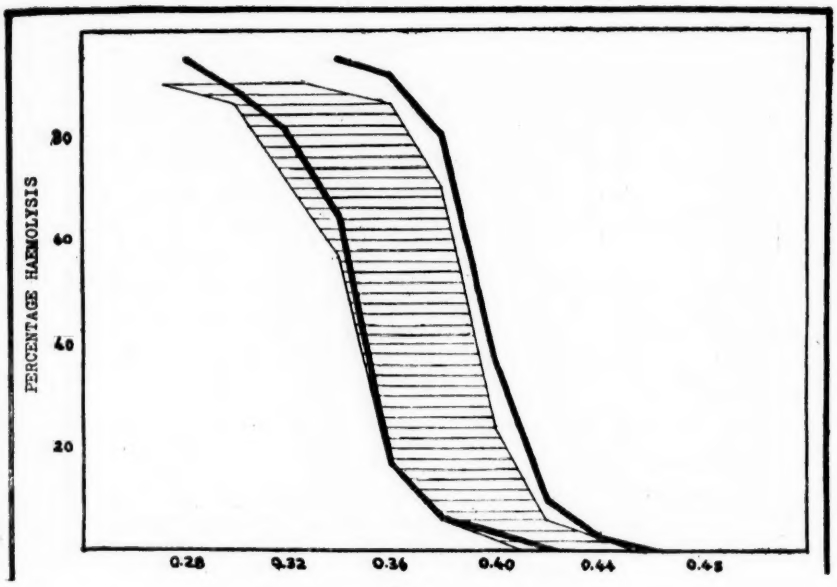

FIG. 2.

PERCENTAGE NaCl CONCENTRATION

Range of red cell fragility within which fall 20 cases of normal pregnancy (cases with haemoglobin 80 per cent and over).

It is to be noted that the standard deviation and variability per cent are within normal limits in some of the "anaemic" group. The degree of anisocytosis associated with considerable variation in staining density was a striking feature of many of the films. In some cases the dense microcytes characteristic of acholuric jaundice were found. The appearance of the films was suggestive in some cases of a mixed iron and liver deficiency, in others of acholuric jaundice.

The range of red cell fragility in the 28 cases of anaemia of pregnancy is recorded graphically in the composite curve, Fig. 3. Three patients had a median corpuscular fragility greater than the calculated normal and 21 greater than the observed normal. In this chart it is possible to compare the range of fragility for the pregnancy cases with the range for 16 cases of postpartum anaemia. In Fig. 1 the range of median corpuscular fragility in pregnancy anaemia, both the corrected and the uncorrected readings, can be compared with the corrected and uncorrected readings for anaemias of various sorts. From these two figures it is apparent that the red cell fragility in the case of pregnancy anaemia differs from that in most other types of anaemia. In spite of a grade of anaemia which is in most conditions associated with an increased resistance of the red cells (excluding acholuric jaundice) the fragility curve in pregnancy anaemia of even severe grade does not "shift to the left" and in many instances actually shifts to the right. In the majority of cases of anaemia associated with pregnancy after parturition there was a distinct shift to the left of the fragility curve and a decrease in median corpuscular fragility as compared to the antepartum reading (Case

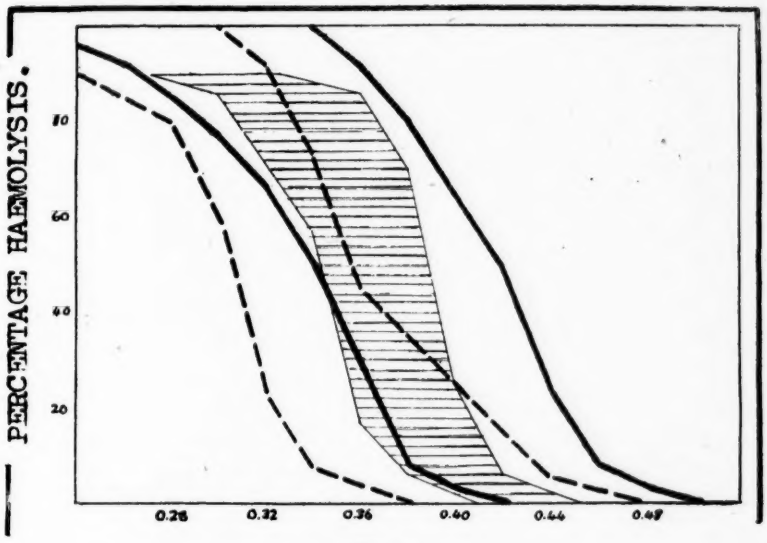

FIG. 3.

PERCENTAGE NaCl CONCENTRATION

Comparison of red cell fragility in pregnancy anaemia, exclusive of cases due to haemorrhage. Solid line shows range of red cell fragility (uncorrected for anaemia) in 28 cases of pregnancy anaemia. Broken line shows range of red cell fragility (uncorrected for anaemia) in 16 cases of postpartum anaemia.

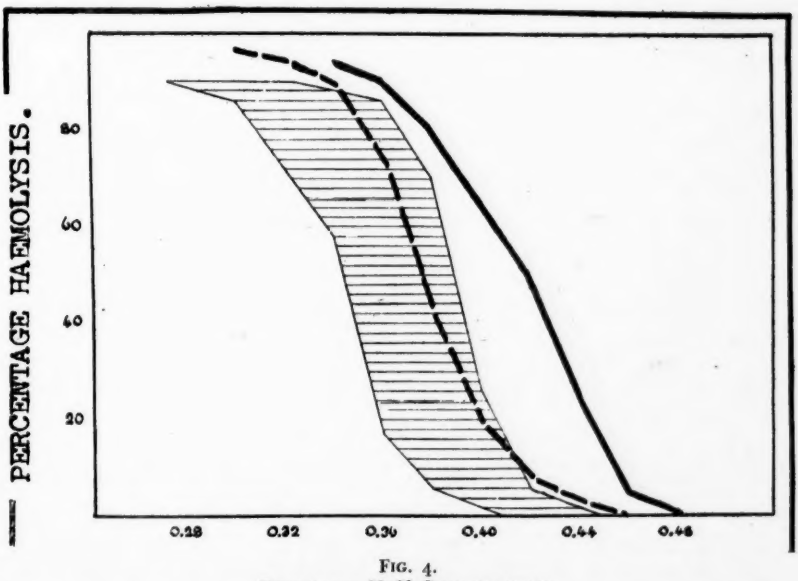

FIG. 4.

PERCENTAGE NaCl CONCENTRATION

(Case 20) Solid line, 34 weeks' antepartum. V.P.C. 26 per cent (uncorrected). Broken line, 4 days' postpartum. V.P.C. 40 per cent (uncorrected). Fragility curves of mother, brother and sister within normal range.

TABLE II.

Haematological Study of 28 Cases of Anaemia of Pregnancy.

Case	R.B.C.	Hb.%	C.I.	M.C.V.	V.P.C.	M.C.D.	M.C.T.	M.C.F.	V.	Sig.	Stage	Treatment
3.	3.80	46	0.6	68	26			0.342			30	Transfusion 1,400 c.c.
								0.358				4 c.c. anahaemin
												Ferri et ammon. cit. gr. 30 t.d.s.
	4.60	78	0.9	84	39			0.369			36	
	4.95	86	0.9	81	40			0.336			8 dys. pp.	
4.	5.00	48	0.5	62	31			0.376			32	Ferri et ammon. cit. gr. 30 t.d.s.
								0.385				
	5.00	52	0.5	62	31			0.360			34	
								0.369				
	5.76	68	0.6	64	37			0.367			36	
	4.76	70	1.0	78	37			0.346			5 dys. pp.	
7.	3.27	32	0.5	66	22	6.3	2.1	0.397	9.1	0.575	39	Transfusion 1,300 c.c.
								0.404				Ferrous sulphate gr. 15 daily
	3.56	42	0.6	70	25			0.392			2 dys. pp.	
								0.397				
	4.70	62	0.7	70	33	6.9	1.9	0.397	13.2	0.911	9 dys. pp.	
								0.402				
	5.75	90	0.8	73	42			0.373			8 wks. pp.	
10.	4.37	76	0.9	74	32			0.358			39	No treatment
11.	4.24	64	0.8	75	32			0.369			37	No treatment
								0.376				
	4.25	62	0.7	73	31			0.336			9 wks. pp.	
13.	4.80	66	0.7	76	37			0.356			37	
								0.362				Ferrous sulphate gr. 15 daily
												Ferrous sulphate gr. 45 daily
	5.40	82	0.8	76	41	7.2	1.9	0.350	8.9	0.637	39	
	4.97	90	0.9	88	44			0.358			8 wks. pp.	

TABLE II (*Continued*)

Case	R.B.C.	Hb.%	C.I.	M.C.V.	V.P.C.	M.C.D.	M.C.T.	M.C.F.	V.	Sig.	Stage	Treatment
15.	4.10	74	0.9	83	34			0.325			28	Ferri et ammon. cit. gr. 30 daily
	4.50	84	0.9	87	39			0.368			38	
17.	4.50	74	0.8	78	35			0.375 0.380			34	Ferri et ammon. cit. gr. 30 t.d.s.
	5.60	88	0.8	80	45			0.371 0.378			38	
18.	4.31	56	0.7	73	32			0.378 0.384			34	Ferri et ammon. cit. gr. 30 t.d.s.
20.	3.50	42	0.6	74	26	6.0	2.6	0.420	13.3	0.798	34	Transfusion 1,650 c.c.
	4.80	82	0.9	83	40	6.5	2.5	0.376	12.6	0.818	7 dys. pp.	Ferri et ammon. cit. gr. 30 t.d.s.
22.	3.28	66	1.0	98	32	7.2	2.4	0.370 0.373	8.4	0.603	36	Hepastab 5 c.c. daily 5 days Ferri et ammon. cit. gr. 30 t.d.s.
	4.88	90	0.9	87	43			0.376			14 wks. pp.	Transfusion
24.	3.80	70	0.9	82	31			0.370 0.380			33	No treatment
	4.68	82	0.9	81	38			0.368			3 wks. pp.	
26.	4.05	68	0.9	81	33			0.356 0.370			36	Ferri et ammon. cit. gr. 30 t.d.s.
	5.00	86	0.9	84	42			0.367			10 wks. pp.	
27.	4.40	70	0.8	74	33			0.348			33	No treatment
28.	4.28	72	0.9	77	33			0.355			22	
29.	4.83	68	0.7	64	31			0.343			30	Ferri et ammon. cit. gr. 30 t.d.s.
	5.10	84	0.8	77	40	7.3	1.8	0.366	8.5	0.625	39	
30.	4.27	66	0.8	77	33			0.388 0.397 0.372			38	No treatment

TABLE II (*Continued*)

Case	R.B.C.	Hb.%	C.I.	M.C.V.	V.P.C.	M.C.D.	M.C.T.	M.C.F.	V.	Sig.	Stage	Treatment
31.	4.64	56	0.6	58	27	6.5	1.7	0.387	10.7	0.700	25	No treatment
	5.15	74	1.1	71	37			0.373			6 wks pp.	Ferri et ammon. cit. gr. 30 t.d.s.
								0.378				
32.	4.27	74	0.9	76	33			0.342			38	Ferri et ammon. cit. gr. 30 t.d.s.
								0.350				
33.	3.55	66	1.0	83	30			0.365			28	Iron
								0.371				
34.	4.33	68	0.8	72	31			0.370			36	
								0.377				
37.	3.56	65	0.9	88	32	7.2	2.1	0.346	6.8	0.495	34	No treatment
								0.358				
40.	3.80	75	0.9	84	32	7.1	2.1	0.360	9.1	0.650	34	No treatment
								0.368				
41.	4.10	75	0.9	84	34	7.1	2.1	0.364	8.5	0.601	36	No treatment
	5.03	86	0.9	79	40			0.367			4 mos. pp.	
42.	3.88	65	0.8	80	31	7.4	1.9	0.360	8.6	0.635	34	No treatment
								0.370				
47.	3.80	60	0.8	74	28			0.386			34	No treatment
								0.397				
50.	4.40	76	0.8	77	34			0.384			39	
	4.93	89	0.9	87	43			0.365			5 wks. pp.	
56.	3.81	68	0.9	88	34			0.344			34	No treatment
								0.356				

20, Fig. 4). The earliest that this change was demonstrated was the 5th day after delivery: it was shown to be delayed at least 9 days in one case. The data are insufficient to say when the change takes place as a rule. In no case was there a significant increase in median corpuscular fragility postpartum, the greatest being 0.008. In the matter of red cell fragility, therefore, anaemia during pregnancy behaves differently from other types of anaemia, exclusive of acholuric jaundice.

As might have been expected a fair degree of correlation was found between median corpuscular fragility and both mean corpuscular thickness and the ratio of mean corpuscular thickness to mean cell diameter (Haden 1934: Dacie and Vaughan 1938: Cassells 1938). For instance in Case 20 with a median corpuscular fragility of 0.420 mean corpuscular thickness was 2.6. In both normal and anaemic patients there was no correlation between median corpuscular fragility and haemoglobin percentage.

In only 2 of the cases of anaemia was the reticulocyte count raised reaching a maximum figure of 4 per cent. One patient had the highest mean corpuscular volume in the series 98 c.μ and failed to respond to either liver or iron, but had a mean corpuscular fragility within normal limits. In the other there was a high median corpuscular fragility. In the series as a whole there was no correlation between median corpuscular fragility and reticulocyte count. Plasma bilirubin fell within normal limits. There was no correlation between median corpuscular fragility and plasma bilirubin.

Treatment and Follow-up Observations.

The majority of patients responded to treatment in an expected manner: Four patients (11, 27, 31, 33) did not receive any treatment during pregnancy. In one (Case 31) iron was given after delivery with a satisfactory response. Nine patients (Nos. 4, 13, 15, 17, 18, 22, 26, 29, 32) were given iron—one patient (No. 22) with an initial colour index of 1 and high mean corpuscular volume failed to respond to both iron or an effective liver extract and was given a transfusion. The patient improved spontaneously after delivery. Six patients showed a definite and typical response to iron. In Case 4, the patient, as might be expected in view of the low colour index, responded to iron and not to an effective liver extract. Three patients (Cases 3, 7, 20), because of the severity of the anaemia, were given immediate drip transfusions and did well.

Discussion.

Two points arise from the above study of the red cell characteristics in the anaemia of pregnancy which have not been previously stressed:

(*a*) There is a significant increase in median corpuscular fragility, thus differentiating the anaemia, irrespective of its other characteristics, from the majority of other anaemias.

(*b*) There is a tendency to an increase in mean corpuscular thickness associated with a high variability and variation in red cell staining.

This increase in median corpuscular fragility was noted in a single case by Cassells (1938), which in view of the high fragility and increased thickness of the cells was actually diagnosed as acholuric jaundice during pregnancy, but the patient made a spontaneous recovery after delivery. Evans and Wills (1939) have noted a similar increase in tropical megalocytic anaemia associated with pregnancy. The figure for men and non-pregnant women in their series was significantly lower than that for pregnant women.

Apart from pregnancy anaemia the only

other conditions in which increased fragility has been noted are acholuric jaundice, certain other haemolytic anaemias and anaemia associated with myelosclerosis and leuco-erythroblastic anaemia (Vaughan and Harrison 1939). In acholuric jaundice increased fragility is associated with increased haemolysis—evidence is not available as to whether increased haemolysis is present in leuco-erythroblastic anaemia. Studies of pigment metabolism in the anaemia of pregnancy are not available but none of the other haematological abnormalities, apart from a slight increase in cell thickness associated with a haemolytic process, are present; there is no rise in reticulocytes or in serum bilirubin. There is, therefore, no explanation at present of the increase in red cell fragility to normal saline which is found in so many cases of anaemia of pregnancy. It is obviously dependent upon the pregnancy as Evans and Wills suggested, since the fragility returns to normal after delivery and a high figure for median corpuscular fragility is also found in pregnancy unassociated with anaemia. The point clearly merits further investigation.

An abnormal degree of anisocytosis was found in many patients with a haemoglobin above 80 per cent who would not be regarded usually as showing any anaemia. It is possible, as suggested by Boycott (1936), that such variability is a more important sign of abnormal haemopoiesis than a low haemoglobin in a group of patients known to have varying degrees of dilution. If this, as the results of further work, should prove correct, it would mean that certain of the patients classified as normal should be grouped among the anaemic and certain of the anaemic returned to the normal. In many patients with high variability and low haemoglobin there was also great variation in the haemoglobin content of the cells, suggesting as is found in gastric disorders (Vaughan 1938) a dual deficiency of iron and the P. A. factor.

Normal Haematological Standards During Pregnancy.

The accepted normal haematological standards for women do not apply to women in the pregnant state owing to the profound physiological alterations in the blood volume which occur during pregnancy.

Blood Volume During Pregnancy.

Willcocks (1881) first suggested that in normal pregnancy the falling red cell count and haemoglobin might be due to a physiological hydraemia. Actual observations on blood volume have since shown that there is an average tendency to an increase of blood volume during pregnancy, the increase amounting to about 25 per cent of normal (Keith, Rowntree and Geraghty 1915: Dieckmann and Wegner 1934a: Richter, Meyer and Bennett 1934: Thomson, Hirsheimer, Gibson and Evans 1938: Burwell 1936, 1938).

The volume tends to diminish about a month before term and returns to normal within a month postpartum. The range of individual observations from which the average figures of various observers are calculated is, however, wide; varying from a minimum of no increase at all in an appreciable number of cases to a maximum of at least 40 per cent above normal. This variability in the degree of dilution must be appreciated in considering its effects on the blood picture.

From an analysis of the large number of observations that have been made upon the haemoglobin level during pregnancy (Kühnel 1927: Galloway 1929: Bland, Goldstein and First 1930b: Strauss and Castle 1932b: Davies and Shelley 1934:

Dieckmann and Wegner 1934b: Richter, Meyer and Bennett 1934: Van Donk, Feldman and Steenbock 1934: Davidson, Fullerton and Campbell 1935: McGeorge 1935: Boycott 1936: Fullerton 1936b: Goodall and Gottlieb 1936: Gottlieb and Strean (1939) it may be concluded that there is a fall in haemoglobin per cent as pregnancy advances, whatever the original level of the haemoglobin, maximal towards the end of the second and the beginning of the third trimester and showing a tendency to rise slightly up to term. Watson (1938) is alone in suggesting that there is a rise in haemoglobin throughout pregnancy. Owing to the factor of blood dilution, the degree of which may be variable, it is difficult to lay down any figure for normal haemoglobin level during pregnancy and varying figures have been accepted by different workers (Dieckmann and Wegner 1934b: Adair, Dieckmann and Grant 1936: Boycott 1936: Bethell 1936: Labate 1940). The lowest acceptable figure is 70 per cent Haldane although many observers consider this too low and prefer to accept a figure of 80 per cent Haldane as has been done in the present paper. Although the haemoglobin percentage falls the total circulating haemoglobin increases by approximately 13 per cent (Dieckmann and Wegner 1934b). The fall in haemoglobin is associated with a fall in total red cell count. Adair *et al.* (1936), from a statistical analysis of several thousand observations, concluded that 3,360,000 per c.c. was the lowest limit of normal. The majority of observers would consider this figure too low and accept one in the neighbourhood of 4,000,000 per c.c. (Strauss and Castle 1932b: Labate 1939). Variable figures have been recorded for the colour index in normal pregnancy—extremes being 1.44 to 0.84 (Bland, Goldstein and First 1930a: Strauss and Castle 1932b: Dieckmann and Wegner 1934b). Fullerton (1936b) stresses that a colour index below normal indicates that there is more than simple hydraemia—probably an iron deficiency anaemia. Boycott (1936) has made the most detailed study of this question. He emphasizes the fact that there may be a low colour index and low haemoglobin without true anaemia where cell measurement shows normal cell size and variability—i.e. when there is no anisocytosis. On the other hand patients may show a similar low colour index associated with considerable anisocytosis—there is then definite evidence of anaemia. As already discussed the present study would appear to substantiate this finding; in other words the appearance of the red cells in stained films may be more significant of disturbed erythropoises than the haemoglobin level. Associated with the increased plasma volume in pregnancy there is usually a fall in the total volume of packed red cells (Plass and Bogert 1924: Skajaa 1929: Van Donk *et al* 1934: Dieckmann and Wegner 1934c: Thomson *et al* 1938: Labate 1940). The minimal figure recorded is about 32 per cent (Plass and Bogert 1924). The mean corpuscular volume appears to increase during pregnancy, ranging from 77 c.μ to 100 c.μ. (Dieckmann and Wegner 1934c: Bethell 1936: Watson 1938). A few figures as high as 120 c.μ have been recorded. No figures for mean corpuscular diameter in pregnant women having a haemoglobin above 80 per cent, except those noted in the present study, are available. The red cell fragility curve in normal pregnancy is within the limits of the calculated normal as shown on p. 201 but the median corpuscular fragility, though within calculated normal figures, is in many cases higher than the observed normal figure. Apart from the figures quoted in the present series figures are not available for reticulocyte counts in normal pregnancy. Figures for plasma bilirubin other than those in the present series are not recorded.

Classification of the Anaemias of Pregnancy.

The following classification of anaemia occurring during pregnancy is suggested. It differs in some respects from that usually given.

I. *Physiological Anaemia.*

II. *Deficiency Anaemia of Pregnancy.*

(*a*) Iron deficiency anaemia.

(*b*) Megalocytic anaemia of pregnancy.
(i) Pernicious anaemia of pregnancy.
(ii) Myeloblastic anaemia of pregnancy and the puerperium.

(*c*) Mixed iron and P.A. deficiency.

III. *Unproven Group.* This group includes a variety of conditions, some unproven, some disproven, but still quoted as clinical entities.

(*a*) Acute haemolytic anaemia of pregnancy.

(*b*) Protein deficiency anaemia of pregnancy (Bethell).

(*c*) Vitamin B deficiency anaemia of pregnancy (Elsom).

IV. *Unclassified Group.* This group includes cases which do not conform to the above groups and yet which on the available evidence can reasonably be considered as possibly due to pregnancy.

V. *Anaemia Complicated by Pregnancy*, including tropical megalocytic anaemia.

I. The Physiological Anaemia of Pregnancy.

The occurrence of some degree of hydraemia during pregnancy and its effect upon the blood picture has already been discussed in relation to normal haematological standards during pregnancy.

It is perhaps possible for a haemoglobin as low as 65 per cent Haldane and a red cell count as low as 3.20 million to be physiological during pregnancy provided certain other conditions are satisfied. These other conditions are: (*a*) the colour index must be near unity; (*b*) the mean cell diameter must be within normal limits; (*c*) the standard deviation and variability, expressing the degree of anisocytosis, must be within normal limits; (*d*) the mean corpuscular volume must be within the normal limits for pregnancy. The cause of the reduction of red cells and haemoglobin percentage in such a case may be the physiological hydraemia of pregnancy, which is well known to vary greatly in its degree. A possible example of this type in this series is Case 37, with haemoglobin 65 per cent, red cells 3.56 million, colour index 0.9, mean cell diameter 7.2 μ standard deviation 0.495, variability 6.8 per cent, mean corpuscular volume 88 cu. μ and no symptoms of anaemia. Conversely, if one of the above conditions is not satisfied in a case with haemoglobin percentage within the range which the most critical observer would consider normal the physiological normality of the blood picture must be doubted. An example of such a case is No. 36, with haemoglobin percentage of 80, mean cell diameter of 6.8 μ standard deviation of 0.509, variability of 7.5 per cent, but colour index of 0.69 and mean corpuscular volume of 62 cu. μ. Unless, however, it is possible to make a detailed blood examination a haemoglobin below 80 per cent Haldane should be regarded with suspicion.

II. Deficiency Anaemia of Pregnancy.

(a) *Iron Deficiency Anaemia.*

Many of the investigations concerned with iron deficiency anaemia of pregnancy

have been badly controlled and only publications dealing with the more satisfactory studies are discussed here. The haematological characters of the anaemia are similar to those seen in any type of iron deficiency anaemia. Strauss and Castle (1932b) described 30 cases in which the colour index lay between 0.47 and 0.71, there was moderate anisocytosis, mean corpuscular volume was below normal, reticulocytes and plasma bilirubin were normal. Response to iron treatment is an important diagnostic aid, especially in the milder cases. The dose of iron must, however, be adequate, namely ammoniated citrate of iron, gr. 90 daily (Strauss and Castle 1932b) ferrous sulphate, gr. 9–15 daily (Fullerton 1934: Corrigan and Strauss 1936: Gottlieb and Strean 1939: Labate 1939) or Blaud's pill, gr. 45 daily (Boycott 1936). A rise in the reticulocyte count is the earliest and most reliable sign that the case is responding to iron and in doubtful cases of iron deficiency it should be looked for between the 4th and 10th day of treatment. The increase in anisocytosis as the case responds may also be of some diagnostic value. It is not of course specific for iron treatment and does not require a Price-Jones curve to be apparent to a moderately experienced observer. The test of the rise in haemoglobin percentage may be unsatisfactory as a guide to the effectiveness of iron treatment, since it is sometimes undesirable to have to wait 2 or 3 weeks for the rise to occur. Several large-scale surveys have demonstrated the value of iron in the treatment of anaemia of this type (Corrigan and Strauss 1936: Fullerton 1936b: Gottlieb and Strean 1939: Labate 1939). Adair *et al* (1936) studied a group of 235 pregnant women and came to a somewhat different conclusion, namely that the rate of improvement was the same in the treated and the untreated group, 65 out of their 74 untreated patients improved spontaneously. Details of the cases are, however, not available. Bethell (1936) concluded that patients who did not respond to iron were suffering from protein deficiency. It seems more likely that this failure was due to the fact that the patients had no true anaemia. Other observations on the value of iron are unsatisfactory as the work has been incompletely controlled (Galloway 1929: Jerlov 1929: Davis and Walker 1934: Richter, Meyer and Bennett 1934).

Aetiology.

In discussing the aetiology of the iron deficiency anaemia of pregnancy the following factors must be considered: (1) pre-existing anaemia; (2) the effect of pregnancy on the hydrochloric acid secretion of the stomach; (3) the influence of social conditions and diet; (4) changes in iron metabolism due to pregnancy; (5) the number of previous pregnancies.

(1) *Pre-existing Anaemia.*

For obvious reasons it is difficult to prove whether a pregnant woman was anaemic before she became pregnant, and precise data on this point is not available. If the return to a normal haemoglobin percentage within a few weeks of delivery in patients showing moderate or severe degrees of anaemia during pregnancy can be taken to indicate that the haemoglobin percentage was normal before pregnancy then the anaemia of pregnancy is not usually associated with pre-existing anaemia (Bland, Goldstein and First 1930b: Watson 1938). Fullerton (1936b) has, however, concluded by deduction that "such anaemias (hypochromic) probably antedate the pregnancy and apparently are rendered more severe by the hydraemia of pregnancy." Strauss and Castle (1932b) conclude that "the existence of anaemia prior to pregnancy apparently

need not condition anaemia of greater degree during pregnancy" as long as an adequate diet is given.

(2) *Secretion of Hydrochloric Acid.*

It is known that iron is more readily absorbed from an acid than from an alkaline medium, hence achlorhydria or hypochlorhydria may be factors favouring the development of an iron deficiency anaemia (Mettier and Minot 1931). There is considerable evidence to suggest that during pregnancy there may be a decrease in the acid secretion of the stomach (Arzt 1930: Strauss and Castle 1932a: Davies and Shelley 1934: Goodall and Gottlieb 1936: Watson 1938). Bethell (1936) did not find any relation between the degree of anaemia and the level of acid, but found the acid reduced in 15 cases examined. It appears probable, therefore, that the temporary alteration in gastric secretion in pregnancy may play its part in favouring the development of anaemia.

(3) *The Influence of Diet and Social Conditions.*

Most of the mass survey investigations, which on first reading indicate poor diet as being an association of anaemia of pregnancy, have been done on populations which are anaemic quite apart from pregnancy. Few of them, if any, are able to prove that the anaemia developing in pregnancy is more than can be accounted for by the hydraemia of pregnancy. Davidson and Fullerton (1933) demonstrated that the diet of 49 families, representative of the general population under investigation, was poor in iron; many hundreds of women of the population, some pregnant and some not, were found to be anaemic, the pregnant women having an average haemoglobin 5 per cent lower than the non-pregnant women for different age groups. The small difference of 5 per cent, if anything, favours hydraemia as the cause of the difference. Fullerton (1936a) taking income level as the standard of dietetic adequacy showed that among 332 pregnant women, 164 with low income levels had an average haemoglobin of 73.1 per cent and 168 with higher income levels had an average haemoglobin of 19.6 per cent. The control group of 140 non-pregnant women showed 87 with low income level to have an average haemoglobin of 83.2 per cent and 43 with higher income level an average haemoglobin of 86.3 per cent. The pregnant women with low income had 6 per cent less haemoglobin than the pregnant women with higher income, while the difference between the non-pregnant low and higher income groups was only 3 per cent. This difference may possibly be significant enough to suggest that the poor group of pregnant women became relatively more anaemic than the better off group, hydraemia alone not being responsible for the greater drop in the poor group. Fullerton (1936b) is of opinion that the lowering of haemoglobin in both groups is due to hydraemia only. Reid and Mackintosh (1937a) found the haemoglobin of 1,108 pregnant women to be under 70 per cent in 10 per cent of the cases, but that the incidence of the lower haemoglobin levels was greater in the lower income groups. There was no control series of non-pregnant women, so that conclusions cannot be drawn from their work as to the effect of pregnancy *per se* Adair *et al.* (1936) found that a group of hospital-class pregnant women was slightly more anaemic than a group of private patients: again, there was no control group of non-pregnant women in each class. Watson (1938) considered diet unimportant, but his figures were based on uncontrolled investigations. Hamilton and Wright (1942) have recently suggested

that women of the artisan class are more anaemic during pregnancy than before the war and attribute this finding to wartime dietary.

The method of mass survey, therefore, is not very helpful in settling the problem of the relation of diet to the development of pregnancy anaemia. It remains once again for detailed study of individual cases to give the necessary information. Strauss and Castle (1932a and b) have shown that a low protein diet, especially when associated with low gastric hydrochloric acid, resulted in a greater loss of haemoglobin in pregnancy than a good diet, and that an adequate diet given during pregnancy to cases previously anaemic will produce an improvement in the anaemia. McCance *et al.* (1938) have shown on small groups of pregnant women that iron intake and haemoglobin levels rise with increasing income. The highest income group had a mean haemoglobin level of 90 per cent compared with a figure of 76 per cent in the lower income group. A level less than 79 per cent was not found in the higher income group. The work of Bethell (1936) on protein deficiency anaemia and the work of Elsom (1935, 1937) on Vitamin B deficiency anaemia of pregnancy is referred to later.

(4) *Changes in Iron Metabolism due to Pregnancy.*

The intake of iron during pregnancy was investigated in 49 families by Davidson and Fullerton (1933). They calculated that the average daily intake was 7.71 mg. for women. Quoting several authorities (Elvehjem *et al* 1933, 1934: Shackleton and McCance 1936: Widdowson and McCance 1936) it was considered that about 75 per cent of this was available and as about 50 per cent is absorbed as a rule (Witts 1936) the amount that the women absorbed averaged 2.5 mg. daily. This is less than half of what is required to maintain a positive balance in the reproductive period. Coons (1935) calculated that in pregnancy an intake of 14.7 mg. daily gives a positive balance of 3.16 mg. McCance *et al.* (1938) concluded from their study of iron intake and haemoglobin levels in pregnant women that a satisfactory daily intake would be 20 mg., i.e. considerably greater than that usually achieved even by women in a high income group.

The iron requirements during pregnancy have been reviewed by Fullerton (1936a) who, quoting many references, and especially the work of Coons (1932, 1935) and taking into consideration every possible debit and credit of iron during pregnancy, delivery, the puerperium and lactating period, concluded that during pregnancy the extra demand for iron is 2 mg. per day. The maternal tissues require no more than in the non-pregnant state: the whole extra requirement is for the foetus and to make up for the blood lost at delivery. The amount of iron in the blood during pregnancy has been investigated by Sachs (1936) who found that it was reduced below the level for non-pregnant women, the figures being 40 and 45 mg. per cent respectively.

The foetal demands for iron as measured by the amount of iron storage in the foetal liver at different stages of gestation have been shown to be greatest in the last trimester both in animals (Bunge 1889) and humans (Hugonenq) 1899). The foetal haemoglobin percentage, which is an additional reflection of the foetal requirements, increases rapidly in the early part of the last trimester: in the rat foetus (Nicholas 1928) the rise is from 5 to 9 grammes per cent in the early part of the third trimester, and in the rabbit foetus (Zeidberg 1929) the rise is from 8 to 12 grammes per cent during the whole of the last trimester. It may be concluded, therefore, that there is increased

demand for iron during pregnancy due to the requirements of the foetus, though this is made up for to some extent by the cessation of menstruation.

(5) *The Number of Previous Pregnancies.*

There is considerable disagreement as to the effect of the number of pregnancies on haemoglobin level. Reid and Mackintosh (1937a) believe that though multiparity in good social circumstance is without effect except in women with 5 or more pregnancies, it is associated with increased anaemia in lower income groups. Fullerton (1936a) on the other hand thinks the effect of parity is really an effect of age; the number of pregnancies in his view is likely to be increased in the older age group who even when unmarried show a falling haemoglobin. When the balance sheet of iron intake and iron loss is taken into account, especially the iron that may be lost at parturition, it would be expected that in the low income group where iron intake is low there should be an increased degree of anaemia.

From the above discussion it is clear that there are factors operative, quite apart from the normal effect of dilution during pregnancy, which may under certain conditions cause anaemia; it is also clear that many cases of so-called iron deficiency anaemia of pregnancy are really iron deficiency anaemias of some standing which are first noticed during pregnancy. In either case it is most essential to ensure an adequate diet, if necessary supplemented by iron therapy, to all pregnant women.

(b) *The Megalocytic Anaemias of Pregnancy.*

Considerable confusion exists in the literature concerning the megalocytic anaemias of pregnancy. In the past any severe anaemia associated with pregnancy has only too often been described as pernicious anaemia of pregnancy. It is probably wise not to attempt to classify many of these cases as the data given are in most cases insufficient to enable a satisfactory diagnosis to be made. Two possible distinct groups may be differentiated:

(i) Pernicious anaemia of pregnancy.

(ii) Megaloblastic anaemia of pregnancy and the puerperium.

(i) *Pernicious Anaemia of Pregnancy.*

The term pernicious anaemia of pregnancy has been used rather loosely in the literature. The definition of Vaughan (1936) affords a reasonable basis upon which to build a clinical entity, namely "a megalocytic, hyperchromic anaemia occurring during pregnancy or the puerperium, not necessarily associated with achlorhydria, due to a temporary deficiency of P.A. factor." A corollary to this definition should be that the blood responds to liver extracts, and that the response should include a reticulocyte crisis to exclude so far as possible the response being coincidental; other causes of megalocytic anaemia must be excluded.

The number of recorded cases satisfying these criteria is small, since it is now agreed that the severe megalocytic anaemia occurring in tropical countries is not caused by pregnancy but is only complicated by pregnancy (Wills 1934). The most convincing and the largest series of cases reported are the 8 of Strauss and Castle (1933). In these the colour index varied from 1.0 to 1.25, mean corpuscular volume 105 to 130 cu. μ, there were in stained films microcytes, macrocytes and tailed forms, and morphologically the blood picture was "similar to true pernicious anaemia." There was complete achlorhydria to histamine in 2, and

one of these two had normal gastric hydrochloric acid 2 years later: in 4 the gastric hydrochloric acid was low. Subsequent treatment, after parturition, was not necessary to prevent relapse.

Larrabee (1925) is often quoted for his description of 8 cases of "pernicious anaemia of pregnancy." Seven were studied for the first time postpartum, the only standard of macrocytosis being the colour index. Two apart from response to liver conformed to modern definition, the remaining 6 were on the evidence given more likely pregnancy associated with pernicious anaemia. Other cases which were probably pernicious anaemia due to pregnancy have been described by Rowland (1924), Peterson, Field and Morgan (1930), Wilkinson (1932), Whitby (1932), Rowland (1933), Studdiford (1934), Atkin (1938), Ritter and Crocker (1939). Numerous cases have been reported as pernicious anaemia of pregnancy and handed down from author to author as such without any attempt to criticize the diagnosis. It is impossible on the data given to classify such cases in a satisfactory manner (Channing 1842: Beckmann 1921: Esch 1921: Hampson and Shackle 1924: Smith 1925: Hoskin and Ceirog-Cadle 1927: Allan 1928: Evans 1929: Kersley and Mitchell 1934: Lull 1937: Stevenson 1938). This type of anaemia is obviously rare though few figures are available to indicate its true incidence. Boycott (1936) did not note any case in 222 pregnant women examined haemotologically and Reid and Mackintosh (1937a) did not find any instances in 1,108 pregnancies. The majority of surveys have concentrated on average figures and therefore cases of macrocytosis tend to get lost. The work of Strauss and Castle (1933) indicates that the cause of the anaemia is a failure to produce the P.A. principle through lack of either extrinsic or intrinsic factor or a combination of both factors.

(ii) *Megaloblastic Anaemia of Pregnancy and the Puerperium.*

Davidson, Davis and Innes (1942) have recently described a group of 16 cases of severe anaemia during pregnancy or the puerperium which were distinguised by the 'megaloblastic'* reaction of the marrow found on sternal puncture. Basing a diagnosis solely on the peripheral red cell picture the authors would have considered 5 of the cases to be classical pernicious anaemia while the others had one or more of the characteristic features missing—in many instances the colour index was below unity. The outstanding features differentiating the cases from Addisonian pernicious anaemia were the presence of free hydrochloric acid in the gastric juice and a lower frequence and degree of macrocytosis and ovulocy-

* Considerable confusion has arisen in the past over the term megaloblastic reaction. It is used here in the same sense as that understood by Davidson, Davis and Innes (1943). "The recognition of megaloblastic erythropoiesis is based upon the presence in the marrow smear of a greatly increased frequency of the primitive basophil erythroblasts (Type I cells). Type II cells are also numerous. These may show varying degrees of cytoplasmic ripening (haemoglobination) and are characterized by the loosely reticulated, open-work structure of the nuclei, which present an appearance quite distinct from the lumpy condensed nuclei of the erythroblasts of equivalent degrees of haemoglobination seen in a normoblastic marrow.

A marrow smear displaying normoblastic erythropoiesis is one in which the vast majority of the red-cell precursors have compact condensed nuclear chromatin. An occasional primitive basophil erythroblast with a primitive finely reticulated nucleus may be seen, but the remaining erythroblasts, which may include a proportion of cells with basophil cytoplasm varying with the degree of type of anaemia present, are characterized by nuclei displaying lumpy, heavy chromatin patterns, the degree of condensation of which increases with the haemoglobination of the cytoplasm."

tosis. Examination of the sternal marrow revealed, with one exception, a picture identical with that found in Addisonian pernicious anaemia, suggesting that the immediate cause of the anaemia is maturation arrest of the megaloblast. Ten of the cases were refractory to treatment with all forms of liver extract for longer or shorter periods before they responded. Recovery has appeared complete and further treatment has proved unnecessary. The authors suggest that the anaemia is dependent on a lack of the P.A. principle and also on a failure at present unexplained to utilize this factor even if it is made available. They would describe all cases of megalocytic anaemia of pregnancy within this group, including those described above, as pernicious anaemia of pregnancy.

More recently Fullerton (1943) has described 3 somewhat similar cases, the patients responded poorly to liver extracts but improved when whole liver was given in addition to extract, suggesting that some factor in addition to the P.A. factor is lacking. It is possible that Case 22 of the present series should be included in this group.

It is clear that much more careful and detailed work is required to elucidate the aetiology of these severe megalocytic anaemias found in pregnancy that fail to react to liver extracts or iron. From a practical point of view it is essential to remember that they may prove refractory for several months to all known haemopoietic principles, and repeated blood transfusions are essential (Davidson *et al* 1942).

(c) *Mixed Iron and P.A. Deficiency Anaemia of Pregnancy.*

Strauss and Castle (1933) have shown that certain cases of anaemia of pregnancy may be due to a deficiency of both iron and the P.A. principle.

III. Unproven Group.

(a) *Acute Haemolytic Anaemia of Pregnancy.*

More confusion has arisen around the subject of acute haemolytic anaemia of pregnancy than around any other form of pregnancy anaemia. The term is frequently still used synonymously with pernicious anaemia of pregnancy. Allan (1928) speaks dogmatically of the "pernicious anaemia of pregnancy as an acute haemolytic anaemia." With more modern concepts of haemolysis it might be expected that such statements would no longer be used, but as recently as 1938, Stevenson, in presenting 30 cases of alleged pernicious anaemia of pregnancy stated and accepted the dictum of "some writers" (Witts and Wilkinson) who "refer to the condition as the haemolytic anaemia of pregnancy."

The characteristics of an acute haemolytic anaemia are usually given as a rapidly advancing anaemia, with pyrexia, leucocytosis with appearance of premature cells of myelocytic type, increase in nucleated red cells, a persistently raised reticulocyte percentage, and usually, though not invariably, an increased amount of circulating bilirubin. The excretion of faecal urobilin is increased to many times the normal, and is probably the only true criterion of *in vivo* haemolysis (Vaughan and Saifi 1939). The condition may be self-limited, or may terminate fatally; treatment is by blood transfusion and is often effective.

The number of cases in the literature of anaemia in pregnancy that conform to the definition, exclusive of the urobilin excretion, which is rarely available, is remarkably small. Witts (1932) reviewed the literature exhaustively, but accepted cases on insufficient evidence. The cases here detailed were all accepted by him without question. Peterson, Field and Morgan

(1930) describe a case (Case 1 of their series of 4) in which at 3 weeks before parturition there was a red cell count of 0.96 million, haemoglobin 33 per cent, colour index of 1.5, white cell count of 13,000 with a normal differential count, one nucleated red per 100 white cells and 10 per cent of reticulocytes. The van den Bergh test was not recorded. While the raised reticulocyte count was suggestive, there is enough in the rest of the blood count to throw doubt on the diagnosis of acute haemolytic anaemia. The blood recovered after parturition, but it was impossible to say whether the recovery was spontaneous or due to liver or to blood transfusion. Evans (1939) describes a patient seen on the 7th day postpartum with a blood count of 0.9 red cells, haemoglobin 12 per cent, colour index 0.7, white cells 7,000 with 7 per cent of myelocytes, 5 nucleated reds per 200 whites: reticulocytes not counted at that time. Four days later, red cell count 1.0 million, haemoglobin 14 per cent, white cells 14,000 with a few myelocytes, 28 nucleated reds per 200 whites, reticulocytes 40 per cent, and van den Bergh 1.0 mg. per cent. Ten days later, red cells 3.5 million, haemoglobin 30 per cent, white cells 4,000 and reticulocytes 20 per cent. Recovery proceeded, reticulocytes falling to normal in another 10 days. Evans himself suggests that there was no evidence of haemolysis. The red cell fragility was normal at the height of the anaemia. Hampson and Shackle (1924) are also quoted by Witts; reference to their original description does not show any features even suggestive of an haemolytic anaemia. The case has been referred to in the discussion on macrocytic anaemia of pregnancy. Minot (1921) described a patient suffering from jaundice, splenomegaly, increased red cell fragility, reticulocyte count persistently above 20 per cent, and Larrabee (1925) a similar case of "a typical anaemia of pregnancy cured by splenectomy." Both these cases had the features of haemolytic anaemia, but the more reasonable diagnosis seems to be acholuric jaundice complicated by pregnancy. Witts had to go back to the year 1914 to find his best case description as reported by Jungmann (1914). The condition spontaneously recovered after parturition. Many of the features of acute haemolytic anaemia are present, including the high leucocytic count, high nucleated red count, and progressive advance of the anaemia followed by steady recovery. These features alone, however, cannot allow of the case being accepted with any degree of certainty as a case of acute haemolytic anaemia of pregnancy.

Conditions certainly occur which simulate in greater or less degree the usual description of acute haemolytic anaemia of pregnancy. A haemolytic crisis of acholuric jaundice may occur during pregnancy. Acute haemolytic anaemia, such as follows the use of the sulphonamides (Elliott 1939) or other drugs, or acute haemolytic anaemia due to subtertian malaria, may also occur. Such factors unassociated directly with pregnancy should always be sought in a suspected case. Secondly, there are many blood conditions which simulate haemolytic anaemia, for instance acute leukaemia, which can occur coincidentally with pregnancy.

It is significant that in the literature of the last 10 years, not one example of acute haemolytic anaemia of pregnancy has been found.

(b) *Protein Deficiency Anaemia of Pregnancy.*

Bethell (1936) has described an anaemia of pregnancy characterized by a colour index near unity, a high normal or increased mean corpuscular volume (up to 108 cm. μ). He found 6 such cases in a total

of 66 pregnant women examined. The patients failed to respond to iron but improved on a high protein diet. He also found an inverse ratio between the serum albumin fraction and the mean corpuscular volume. Apart from Fullerton's observation that certain patients improved when given whole liver as opposed to liver extract this work awaits confirmation.

(c) *Vitamin B Deficiency Anaemia of Pregnancy.*

Elsom (1935, 1937) claims to have produced a macrocytic anaemia in pregnant women with a diet deficient in vitamin B. The experiment was carried out in the United States on white women. A group of 8 women, in early normal pregnancy, was put on a vitamin B deficient diet, and a group of 3 on a full diet as control. The control group remained normal throughout pregnancy and the puerperium. The test group, about the 8th month of pregnancy, developed clinical symptoms of vitamin B deficiency and the blood picture changed from the initial average values of 3.93 million red cells, 12.8 grammes haemoglobin and mean corpuscular volume of 100 cu. μ to 3.23 million red cells, 12.0 grammes haemoglobin and mean corpuscular volume of 121 cu. μ with reticulocytes up to 3.5 per cent. All returned to normal, clinically and haematologically, as soon as brewers' yeast was administered. After the institution of brewers' yeast treatment, the reticulocytes rose in some to 5.4 per cent and then fell to normal level. The figures of red cell count, haemoglobin and mean corpuscular volume quoted, and the detailed figures in the original case protocols, barely justify Elsom's dogmatic conclusions. The work has not been confirmed, but is interesting in relation to tropical megalocytic anaemia and its cure by marmite.

IV. Unclassified Group.

It is clear from the above discussion that there is a group of anaemias occurring in pregnancy which it is difficult to fit into any known classification. For instance there is little evidence that many of the so-called 'haemolytic anaemias of pregnancy' are really haemolytic. Further there are cases such as Case 22 in the present series which though megalocytic do not respond to the P.A. principle. Further careful analysis of all haematological features has shown that cases such as No. 20 in the present series which, in a large scale survey might, in view of the low haemoglobin level, be classified as an iron deficiency anaemia, show features very unlike those of the classical iron deficiency anaemia, namely, a mean corpuscular volume high for the colour index and a considerably increased median corpuscular fragility.

V. Anaemia Complicated by Pregnancy.

In every case of anaemia, mild or severe, occurring during pregnancy, the possibility of the pregnancy being coincidental must be considered. A person suffering from any particular blood disease may become pregnant, or a pregnant woman may develop any blood disease or disorder during her pregnancy. Only the commoner types will be considered here.

(a) *Anaemia Due to Haemorrhage.*

Occult haemorrhage, especially from the gastro-intestinal tract, may insiduously produce an anaemia during pregnancy. A woman who has haemorrhoids is more likely to bleed during pregnancy. Case 29 is an example of such an anaemia: it was interesting that the red cell fragility in this case afforded a clue indicating that the case was not one of anaemia due to pregnancy. Haematologically it is impossible in many cases to differentiate between the blood

pictures of iron deficiency anaemias and of chronic blood loss. Other lesions, such as ulcer or diaphragmatic hernia, may be the source of occult continuous haemorrhage.

(b) *Addisonian Pernicious Anaemia.*

Wilkinson (1932) described 3 cases of pregnancy occurring in Addisonian pernicious anaemia. In most cases the diagnosis is not difficult. The older age, the regular occurrence of achylia gastrica, the presence of nerve complications, and the permanent liver requirements differentiate it from the pernicious anaemia of pregnancy due to temporary inhibition of P.A. factor.

It must, however, be remembered, that true Addisonian pernicious anaemia may pass through a temporary phase of spontaneous improvement after parturition. It is necessary, therefore, to make regular observations of the blood of apparent cases of pernicious anaemia of pregnancy for many months after parturition.

(c) *Iron Deficiency Anaemia.*

The subject of pre-existing anaemia in cases of iron deficiency anaemia of pregnancy has been fully discussed. It was concluded that an iron deficiency anaemia of pregnancy was more than an aggravation of a pre-existing anaemia of the same type. The majority of cases are, however, probably cases of pregnancy occurring in persons suffering from deficiency hypochromic anaemia. In such cases, as has been pointed out by Strauss and Castle (1932b), there need not necessarily be an aggravation of the anaemia during pregnancy, provided the patient is kept on an adequate diet with a high iron and protein content.

(d) *Tropical or Nutritional Megalocytic Anaemia.*

The relation of this type of anaemia as seen in India (Balfour 1927: MacSwiney 1927: Wills and Mehta 1930: Wills and Talpade 1930: Wills 1931, 1933: Wills and Evans 1938: Napier 1939) to that seen in Macedonia (Fairley *et al* 1938: Foy and Kondi 1939) is still uncertain. In both countries pregnancy acts as a precipitating and complicating factor but is not the cause of the anaemia. Available figures in India suggest that in spite of the predisposing effect of pregnancy the incidence and the haematological and clinical picture is practically the same in both sexes (Wills 1934). Foy and Kondi (1939) suggest there are differences in the response to treatment in men and pregnant women in Macedonia. The anaemia is hyperchromic and megalocytic, there is a high degree of anisocytosis and poikilocytosis—free hydrochloric acid is present in the gastric juice—the serum bilirubin is normal unless there is chronic malaria as a complication. In cases associated with pregnancy, Evans and Wills (1939) have described an increased red cell fragility to normal saline.

The anaemia in pregnant women, all workers are agreed, is cured by the administration of the less pure liver extracts (campolon or hepastab) and by autolysed yeast products. The response to anahaemin or highly purified extract is still controversial (Wills and Evans 1938: Napier 1939: Foy and Kondi 1939: Fairley 1940).

A similar haematological picture has been produced by Wills in monkeys by feeding them on a diet deficient in protein and Vitamin B. There is no doubt that a dietary deficiency plays its part in the aetiology of the disease; whether the missing factor is one or many remains to be determined. In Macedonia, at least, chronic malaria with a consequent hypertrophied reticulo-endothelial system is also an aetiological factor. Associated with pregnancy this type of anaemia is a serious condition, having in India a maternal mortality of 40 per cent and a foetal mortality of 63 per cent.

(e) *Haemolytic Anaemias.*

It is probable, on the evidence available, that cases of true haemolytic anaemia occurring during pregnancy are not "due" to pregnancy, but are cases of acholuric jaundice or other recognized form of haemolytic anaemia with pregnancy occurring coincidentally. Attention is once more drawn to 2 reported cases, that of Minot (1921) and that of Larrabee (1925) both of which cannot be excluded from the category of acholuric jaundice.

(f) *Miscellaneous Blood Diseases.*

Acute leukaemia occurring during pregnancy has been described (Hampson and Shackle 1924: Richter, Meyer and Bennett 1934) simulating some form of pregnancy anaemia. With modern methods of haematological technique, including examination of the sternal bone marrow, the diagnostic difficulties should not be great.

Aplastic anaemia, purpura haemorrhagica and "splenic anaemia" may present problems of differential diagnosis occasionally.

Symptomatology.

The symptoms of anaemia of pregnancy are those common to any form of anaemia, namely, shortness of breath on exertion, swelling of the ankles, faintness, giddiness, and pallor. These symptoms may appear at any stage of the pregnancy but are not usually noticed before the 6th month.

Purpuric manifestations are described, but usually in cases in which the diagnosis of anaemia of pregnancy is in question. Retinal haemorrhages are found in the pernicious anaemia of pregnancy, but generalized purpura and a haemorrhagic tendency should suggest the possibility of a blood disorder not due to pregnancy but complicated by pregnancy.

Splenomegaly of moderate degree is fairly common in either the iron deficiency anaemia or the pernicious anaemia of pregnancy. Glossitis is not infrequent. Nerve degeneration, however, does not occur and the presence of symptoms or signs of nerve lesion indicate a revision of the diagnosis of the anaemia of pregnancy. A peculiar "watery" complexion is common, probably due to the association of anaemia with hydraemia.

There is, clearly, no symptomatology specific for the anaemia of pregnancy.

Treatment.

Iron Deficiency Anaemia responds well to iron. The dose must be adequate ammoniated citrate of iron, gr. 20 daily (Strauss and Castle 1932b) ferrous sulphate, gr. 9–15 daily (Gottlieb and Strean 1929: Fullerton 1934: Corrigan and Strauss 1936: Labate 1939) or Blaud's Pill, gr. 45 daily (Boycott 1936) are usually adequate. The patient should also be ensured a good mixed diet.

Pernicious Anaemia of Pregnancy by definition responds to P.A. principle given in the form of liver extract by intramuscular injection (Wilkinson 1932).

Megaloblastic Anaemia. This type of anaemia may respond to whole liver (Fullerton 1943) or in some instances to liver extract (Davidson *et al* 1942). Many cases, however, respond only to massive and repeated transfusion of whole blood preferably given at a drip rate (Davidson *et al* 1942).

Tropical Megalocytic Anaemia Associated with Pregnancy responds to crude liver extracts such as campolon or hepastab but the value of the more purified preparations like anahaemin is doubtful (Wills and Evans 1938). Marmite is also extremely effective in this form of anaemia. Large

doses are essential; 30 *g.* a day gives a margin of safety (Wills 1933).

Unclassified Anaemias of Pregnancy. There is clearly a group of anaemias during pregnancy which are at present difficult to classify and which do not fall into any clear cut group. The patients do not respond to known haemopoietic remedies. In such cases use must be made of repeated blood transfusions preferably given at a drip rate.

The Influence of Anaemia of Pregnancy on Maternal and Infantile Health.

Investigations on the influence of anaemia on maternal and infantile health have been concerned either with iron deficiency anaemias only or with large surveys in which iron deficiency anaemias predominate.

Effects on Mother.

Maternal mortality is probably unaffected by the presence of anaemia other than the severe megalocytic forms (Douglas and McKinlay 1935: Reid and Mackintosh 1937: Davidson *et al* 1942). Maternal morbidity (puerperal sepsis) is possibly slightly higher in the anaemic than in the non-anaemic group (Mackay 1935: Reid and Mackintosh 1937b: Labate 1939). The evidence on this point is not, however, very satisfactory. Postpartum haemorrhage is no more severe in anaemic than non-anaemic women (Fullerton 1936b: Reid and Mackintosh 1937b). Stillbirths have been noted to be slightly more common among anaemic women (Reid and Mackintosh 1937b). The incidence of abortions has been noted to be increased in women with hook-worm anaemia (King 1929), which is really an iron deficiency anaemia.

Effects on Infant.

Infants born of even the most severely anaemic mothers are rarely if ever anaemic at birth, but develop anaemia, probably due to deficient iron storage in the foetal liver during the first year of life (Mackay 1931: Abt and Nagel 1932: Parsons 1932, 1936: Strauss 1933, 1935: Toverud 1935: Smallwood 1936: Alt 1938: Gottlieb and Strean 1939). Fullerton (1937) alone records finding no relation between the degree of maternal and infantile anaemia. Infants born of anaemic mothers have a slightly higher morbidity and mortality rate during the first year than infants born of non-anaemic mothers (Mackay 1931: Reid and Mackintosh 1937b). In tropical megalocytic anaemia the foetal mortality rate is 63 per cent.

Summary.

(1) Haematological observations have been made upon 20 pregnant women with a haemoglobin above 80 per cent (Haldane) and upon 28 pregnant women with a haemoglobin below 80 per cent. The findings largely confirmed those of other workers.

(2) The median corpuscular fragility to normal saline was on the upper limits of normal in both groups. In the anaemic group in some instances it was outside normal limits, returning to normal after delivery. This is unlike the majority of anaemias. The significance of this finding is discussed.

(3) The literature concerned with the blood picture in normal pregnancy is reviewed.

(4) A modification of the present classification of the anaemias of pregnancy is suggested in association with a review of the literature.

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BIBLIOGRAPHY.

Abt, A. F. and B. R. Nagel. *Journ. Amer. Med. Assoc.*, 1932, xcviii, 2270.

Adair, F. L., W. J. Dieckmann, and K. Grant. *Amer. Journ. Obstet. and Gynecol.*, 1936, xxxii, 560.

Atkin, I. *Lancet*, 1938, i, 434.

Allan, W. *Surg., Gynecol. and Obstet.*, 1928, xlvii, 669.

Alt, H. L. *Amer. Journ. Dis. Childr.*, 1936, lvi, 975.

Arzt, F. *Amer. Journ. Obstet. and Gynecol.*, 1930, xx, 382.

Balfour, M. I. *Ind. Med. Gaz.*, 1927, lxii, 491.

Beckmann, M. *Monat. f. Geburtsh. u. Gynäk*, 1921, lvi, 119; quoted by Stevenson, 1938.

Bethell, F. H. *Journ. Amer. Med. Assoc.*, 1936, cvii, 564.

Bland, P. B., L. Goldstein, and A. First. *Amer. Journ. Med. Sci.*, 1930a, clxxix, 48.

Bland, P. B., Goldstein, L., and A. First. *Surg., Gynecol. and Obstet.*, 1930b, l, 954.

Boycott, J. A. *Lancet*, 1936, i, 1165.

Bunge, G. *Hoppe-Seyl. Zeitschr.*, 1889, xiii, 399; quoted by Mackay, 1931.

Burwell, C. S. *South. Med. Journ.*, 1936, xxix, 1194.

Burwell, C. S. *et al. Arch. Int. Med.*, 1938, lxii, 979.

Cassells, D. A. K. *Journ. Path. and Bact.*, 1938, xlvii, 603.

Channing, W. *New Engl. Journ. Med. and Surg.*, 1842, i, 157; quoted by Evans, 1929.

Cohen, M. E. and K. J. Thomson. *Journ. Amer. Med. Assoc.*, 1939, cxii, 1556.

Coons, C. M. *Journ. Biol. Chem.*, 1932, xcvii, 215.

Coons, C. M. *Oklahoma. Agric. Expt. Sta. Bull.*, 1935, No.223; quoted by Fullerton, 1936a.

Corrigan, J. C., and N. B. Strauss. *Journ. Amer. Med. Assoc.*, 1936, cvi, 1088.

Dacie, J. V. and J. M. Vaughan. *Journ. Path. and Bact.*, 1938, xlvi, 341.

Davidson, L. S. P., *et al., Brit. Med. Journ.*, 1933, i, 685.

Davidson, L. S. P., L. J. Davis, and J. Innes. *Brit. Med. Journ.*, 1942, ii, 31.

Davidson, L. S. P., L. J. Davis, and J. Innes. *Edinb. Med. Journ.*, 1943, l, 226.

Davidson, L. S. P., H. W. Fullerton, and R. M. Campbell. *Brit. Med. Journ.*, 1935, ii, 195.

Davies, D. T. and U. Shelley. *Lancet*, 1934, ii, 1094.

Davis, M. and E. W. Walker. *New Engl. Journ. Med.*, 1934, ccx, 1315.

Dieckmann, W. J. and C. R. Wegner. *Arch. Int. Med.*, 1934a, liii, 71.

Dieckmann, W. J. and C. R. Wegner. *Arch. Int. Med.*, 1934b, liii, 188.

Dieckmann, W. J. and C. R. Wegner. *Arch. Int. Med.*, 1934c, liii, 345.

Douglas, C. A. and P. L. McKinlay. "Report on Maternal Morbidity and Mortality in Scotland." Edinburgh: H.M.S.O.

Elliott, G. A. *South Africa Med. Journ.*, 1939, xiii, 641.

Elsom, K. O. *Journ. Clin. Investig.*, 1935, xiv, 40.

Elsom, K. O. *Journ. Clin. Investig.*, 1937, xvi, 463.

Elvehjem, C. A., E. B. Hart, and W. C. Sherman. *Journ. Biol. Chem.*, 1933, ciii, 61.

Elvehjem, C. A., E. B. Hart, and W. C. Sherman. *Journ. Biol. Chem.*, 1934, cvii, 383.

Esch, P. *Zentralb. Gynäk.*, 1921, xlv, 341; quoted by Evans, 1929.

Evans, B. D. F., and L. Wills. *Journ. Path. and Bact.*, 1939, xlviii, 437.

Evans, W. *Lancet*, 1929, i, 14.

Fairley, N. H. *Lancet*, 1940, i, 1118.

Fairley, N. H., R. J. Bromfield, H. Foy, and A. Kondi. *Trans. Roy. Soc. Trop. Med. Hyg.*, 1938, xxxii, 132.

Feldman, H., E. C. Van Donk, H. Steenbock, and E. F. Schneiders. *Amer. Journ. Phys.*, 1936, lxix, 115.

Foy, H. and A. Kondi. *Lancet*, 1939, ii, 360.

Fullerton, H. W. *Edinb. Med. Journ.*, 1934, xli, 99.

Fullerton, H. W. *Brit. Med. Journ.*, 1936a, ii, 523.

Fullerton, H. W. *Brit. Med. Journ.*, 1936b, ii, 577.

Fullerton, H. W. *Arch. Dis. Childh.*, 1937, xii, 91.

Fullerton, H. W. *Brit. Med. Journ.*, 1943, i, 158.

Galloway, C. E. *Journ. Amer. Med. Assoc.*, 1929, xciii, 1695.

Goodall, J. R. and R. Gottlieb. *Canad. Med. Assoc. Journ.*, 1936, xxxv, 50.

Gottlieb, R. and G. J. Strean. *Surg., Gynecol. and Obstet.*, 1939, lxviii, 869.

Hamilton, H. A. and H. P. Wright. *Lancet*, 1942, ii, 184.

Hampson, A. C. and J. W. Shackle. *Guy's Hosp. Rep.*, 1924, lxxiv, 193.

Haslewood, G. A. D. and E. J. King. *Biochem. Journ.*, 1937, xxxi, 920.

Hoskin, T. J. and E. Ceirog-Cadle. *Lancet*, 1927, i, 433.

Hugonenq, M. L. *Comp. Rend. Soc. Biol. Paris*, 1899, li, 337; quoted by Mackay, 1931.

Jerlov, E. *Act. Obstet. et Gyn. Scand.*, 1929, viii, 11; quoted by Corrigan and Strauss, 1936.

Jungmann, P. *Munch. med. Wschr.*, 1914, xli, 414; quoted by Witts, 1932.

Keith, N. M., L. G. Rowntree, and J. T. Geraghty. *Arch. Int. Med.*, 1915, xvi, 54.

Kersley, G. D. and D. A. Mitchell. *Brit. Med. Journ.*, 1934, ii, 720.

King, E. L. *Amer. Journ. Obstet. and Gynecol.*, 1929, xviii, 569.

Kühnel, P. *Zeitschr. f. Geburtsh. u. Gynäk.*, 1927, xc, 511; quoted by Adair, Dieckmann, and Grant, 1936.

Labate, J. S. *Amer. Journ. Obstet. and Gynecol.*, 1939, xxxviii, 48.

Labate, J. S. *Amer. Journ. Obstet. and Gynecol.*, 1940, xxxix, 87.

Larrabee, R. C. *Amer. Journ. Med. Sci.*, 1925, clxx, 371.

Lull, C. B. *Med. Clin. North Amer.*, 1937, xxi, 1185.

McCance, R. A., E. M. Widdowson and Verdon Roe. *Journ. Hyg.*, 1938, xxxviii, 396.

McGeorge, M. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1935, xlii, 1027.

Mackay, H. M. M. *M. R. C. Special Report No.* 157, 1931.

Mackay, H. M. M. *Lancet*, 1935, i, 1431.

MacSwiney, S. A. *Ind. Med. Gaz.*, 1927, lxii, 487.

Mettier, S. R. and G. R. Minot. *Amer. Journ. Med. Sci.*, 1931, clxxxi, 25.

Minot, G. R. *Med. Clin. North Amer.*, 1921, iv, 1735.

Mogenson, E. "The size of the red blood cell." 1938, Copenhagen.

Napier, L. E. *Ind. Med. Gaz.*, 1939, lxxiv, 1.

Nicholas, J. S. *Amer. Journ. Phys.*, 1928, lxxxiii, 499.

Parsons, L. G. *Act. Pediatr.*, 1932, xiii, 378; quoted by Alt, 1938.

Parsons, L. G. *Brit. Med. Journ.*, 1936, i, 1009.

Peterson, R., H. Field, and H. S. Morgan. *Journ. Amer. Med. Assoc.*, 1930, xciv, 839.

Plass, E. D. and L. J. Bogert. *Bull. Johns Hop. Hosp.*, 1924, xxxv, 361.

Price-Jones, C. "Red blood cell diameters." 1933, London: Oxford University Press.

Price-Jones, C., J. M. Vaughan, and H. M. Goddard. *Journ. Path. and Bact.*, 1935, xl, 503.

Reid, W. J. S. and J. M. Mackintosh. *Lancet*, 1937a, i, 43.

Reid, W. J. S. and J. M. Mackintosh. *Lancet*, 1937b, ii, 1389.

Richter, O., A. E. Meyer, and J. P. Bennett. *Amer. Journ. Obstet. and Gynecol.*, 1934, xxviii, 543.

Ritter, J. A., and W. J. Crocker. *Amer. Journ. Obstet. and Gynecol.*, 1939, xxxviii, 239.

Rowland, V. C. *Journ. Amer. Med. Assoc.*, 1924, lxxxii, 372.

Rowland, V. C. *Journ. Amer. Med. Assoc.*, 1933, c, 537.

Sacks, A. *Journ. Amer. Med. Assoc.*, 1936, cvii, 569.

Shackleton, L. R. B. and R. A. McCance. *Biochem. Journ.*, 1936, xxx, 582.

Skajaa, K. *Act. Obstet. et. Gyn. Scand.*, 1929, viii, 371; quoted by Dieckmann and Wegner, 1934b.

Smallwood, W. C. *Brit. Med. Journ.*, 1936, ii, 573.

Smith, C. T. *Surg., Gynecol. and Obstet.*, 1925, xl, 223.

Stevenson, E. M. K. *Edin. Med. Journ.*, 1938, xlv, *Trans. Edinb. Obstet. Soc.*, 81.

Strauss, M. B. *Journ. Clin. Invest.*, 1933, xii, 345.

Strauss, M. B. *Internat. Clinics.*, 1935, iv, 56.

Strauss, M. B. and W. B. Castle. *Amer. Journ. Med. Sci.*, 1932a, clxxxiv, 655.

Strauss, M. B. and W. B. Castle. *Amer. Journ. Med. Sci.*, 1932b, clxxxiv, 663.

Strauss, M. B. and W. B. Castle. *Amer. Journ. Med. Sci.*, 1933, clxxxv, 539.

Studdiford, W. E. *Amer. Journ. Obstet. and Gynecol.*, 1934, xxviii, 539.

Thomson, K. J., A. Hirsheimer, J. G. Gibson, and W. A. Evans. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxvi, 48.

Toverud, K. U. *Act. Pediatr.*, 1935, xvii, Suppl. 1, 136; quoted by Alt, 1938.

Van Donk, E. C., H. Feldman, and H. Steenbock. *Amer. Journ. Phys.*, 1934, cvii, 616.

Vaughan, J. M. "The Anaemias," 2nd edition, 1934. London: Oxford Univ. Press.

Vaughan, J. M. *Brit. Med. Journ.*, 1938, ii, 57.

Vaughan, J. M. and C. V. Harrison. *Journ. Path. and Bact.*, 1939, xlviii, 339.

Vaughan, J. M. and G. A. D. Haslewood. *Lancet*, 1938, i, 133.

Vaughan, J. M. and M. F. Saifi. *Journ. Path. and Bact.*, 1939, xlix, 69.

Watson, H. G. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxv, 106.

Whitby, L. E. H. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1932, xxxix, 267.

Widdowson, E. M., and R. A. McCance. *Journ. Hyg.*, 1936, xxxvi, 13.

Wilkinson, J. F. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1932, xxxix, 293.

Willcocks, F. *Lancet*, 1881, ii, 944.

Wills, L. *Brit. Med. Journ.*, 1931, i, 1059.

Wills, L. *Lancet*, 1933, i, 1283.

Wills, L. *Ind. Journ. Med. Res.*, 1934, xxi, 669.

Wills, L. and B. D. F. Evans. *Lancet*, 1938, ii, 416.

Wills, L. and M. M. Mehta. *Ind. Journ. Med. Res.*, 1930, xvii, 777.

Wills, L. and S. N. Talpade. *Ind. Journ. Med. Res.*, 1930, xviii, 283.

Wintrobe, M. M. *Arch. Int. Med.*, 1930, xlv, 287.

Witts, L. J. *Lancet*, 1932, i, 653.

Witts, L. J. *Lancet*, 1936, i, 1.

Zeidberg, L. D. *Amer. Journ. Phys.*, 1929, xc, 172.

A Human Ovum Nine to Ten Days Old

BY

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CLINICAL HISTORY.

THE specimen was obtained from the uterus removed from a married woman, aged 26 years, admitted to hospital for pelvic pain. She had had 2 children, both at term, one in December 1938 and the other in March 1940. She had not had any abortions or miscarriages. At operation on September 9th, 1943, endometriosis of the left ovary was diagnosed and a corpus luteum was seen in the right ovary, but no details of the latter are available. The uterus was placed in 10 per cent formolsaline immediately after removal; later a pin-head red spot was found in the thickened endometrium on the anterior wall of the uterus near the entrance of the right uterine tube; the uterus appeared otherwise normal. A block of tissue surrounding the red spot was removed, appropriately treated, and embedded in paraffin wax. Some sections were removed and only one of these mounted before the true value of the specimen was appreciated. The remainder of the paraffin block was then melted, the tissue orientated and re-embedded, and serial sections 9μ thick were cut, stained with haemalum and eosin and photographed. Study of these revealed that between one-third and one-half of the ovum had been removed in the preliminary treatment but that the remaining portion was sufficient in amount and in excellence of preservation to enable a thorough study of all the various embryonic elements to be made. The menstrual and coital history, summarized in the table, was ob-

Menstrual, coital and operative data. Menstrual cycle 28 days.

Date	Day of cycle	Phenomena	
August 21	1	Menstruation	
24	4		
29	9	(? ovulation)	
30	10	Coitus.....(? Fertilization).....	
31	11	Coitus	
Sept. 1	12	Coitus	Maximum age of embryo 9 to 10 days
2	13	Coitus	
3	14	Coitus	
4	15	Coitus	
7	18	Entered hospital	
9	20	Uterus removed.....	
17	28	End of cycle	
18	1	Expected onset of next menstruation	

tained at the time from both husband and wife. The maximum coital age of the specimen is 9–10 days, an age which is also indicated by the histological structure of the ovum itself.

Histological Examination.

The endometrium (Fig. 2) has the structure characteristic of the secretory (premenstrual) phase of the cycle. It is 5 mm. thick at the implantation site and slightly thinner (4.5 mm.) elsewhere. Compact, spongy and basal strata are clearly differentiated and the " physiological oedema " between the stromal cells is minimal. The endometrial glands are lined by columnar epithelium throughout and contain secretion in the form of an eosinophilic, amorphous coagulum, except in the basal layer where secretion is absent. There is no maternal blood in the glands. Spiral arteries are prominent in the stromal partitions between the glands in the spongy layer, where the glands are tortuous and have the characteristic " saw-tooth " edges. The ovum is embedded solely in the stratum compactum. Definite decidual reaction is not present, but some of the stromal cells adjacent to the trophoblast have a broader halo of perinuclear cytoplasm than ordinary stromal cells (pre-decidual cells).

The trophoblast is clearly differentiated into cytotrophoblast and plasmoditrophoblast (Fig. 1); all stages in the formation of the latter from the former are seen and mitotic figures are numerous in the cytotrophoblast. Solid clumps of cytotrophoblast project from the surface of the chorionic vesicle, but they are not penetrated by the primitive mesoblast, so that true villi are not yet formed. Lacunae of various sizes and stages of formation are present in the plasmoditrophoblast; only those at the abembryonic (superficial) pole of the ovum contain maternal blood, elsewhere they contain only leucocytes. The " operculum," which indicates the site of entry of the ovum into the endometrium, consists of a mixture of fibrin and leucocytes permeated by plasmoditrophoblast; no epithelialization has yet taken place to cover the surface of the operculum. There is no zone of necrosis of the endometrium adjacent to the trophoblast such as was described in the Teacher-Bryce[1] and the Möllendorff Sch.[2] ova, but the stromal cells adjacent to the trophoblast appear to be undergoing cytolysis as they are encroached upon by the trophoblast, and their nuclei show varying degrees of pale staining.

The chorionic cavity (Fig. 1) is permeated by the primitive mesoblast, which has the form of a loose meshwork consisting partly of large stellate cells and partly of smaller elongated cells; the mesoblast is continuous with the cytotrophoblast superficially and with the exocoelomic (Heuser's) membrane deeply. The latter membrane is complete, unlike that in the 11.5 day Hertig-Rock ovum,[3] and, together with the endodermal layer of the germ disc, it encloses the exocoelomic vesicle (primitive yolk-sac). The membrane consists of flattened and elongated cells; it is continuous with the edge of the endodermal layer of the disc, the transition to the cubical endodermal cells being very sudden. This feature favours the view of Heuser[4] that the membrane is mesoblastic in origin, whereas the endoderm is derived from the inner cell mass.

The embryo proper (Fig. 3) consists of a bilaminar disc, comprising a single layer of tall columnar ectodermal cells which form the floor of the amniotic cavity, and a single layer of cubical endodermal cells which form the roof of the exocoelomic vesicle. Mesoderm does not penetrate between these two germ layers. Part of the disc is missing, but assuming it was circular, and such an assumption is warranted by comparison with other early human and with monkey

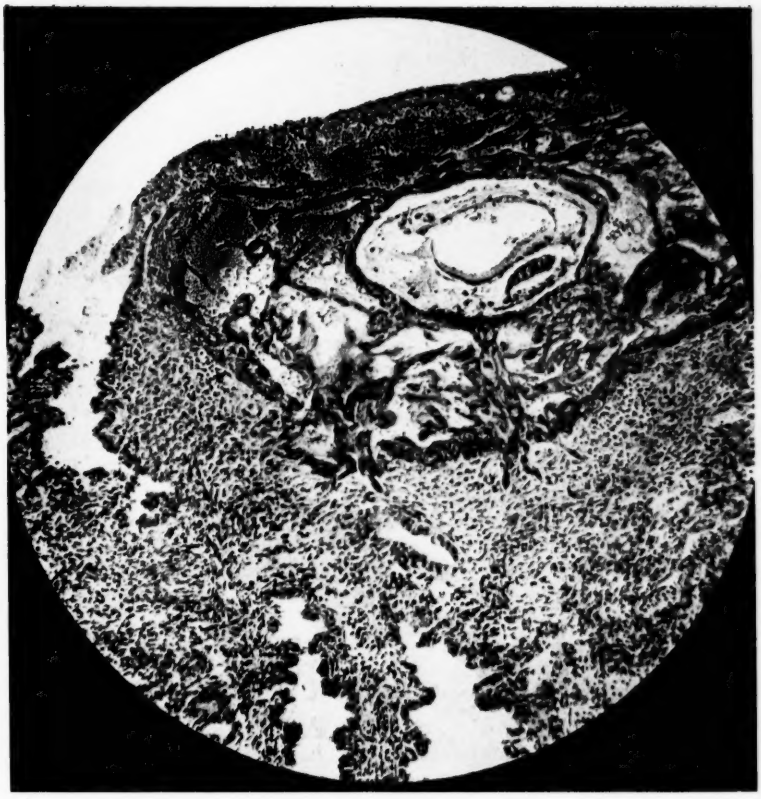

FIG. 1.

Ovum and endometrium. Operculum, consisting of fibrin and leucocytes permeated by plasmoditrophoblast, is seen in upper part of photograph. Fibrinous wisp projects into mouth of gland on left. No epithelium on surface of operculum. Sprouts of trophoblast seen penetrating stratum compactum below ovum. Maternal red-blood corpuscles seen in lucunae of plasmoditrophoblast to left of chorionic vesicle. Primitive mesoblast shown permeating chorionic vesicle between cytotrophoblast and thin exocoelomic membrane. Of the two cavities inside the chorionic vesicle, the upper, larger one is the exocoelomic vesicle (primitive yolk sac), with the endodermal plate of cubical cells forming its lower wall. The lower, smaller cavity is the amniotic cavity; in the picture its upper wall is formed by the columnar cells of the ectodermal disc. The endometrium adjacent to the trophoblast shows no zone of necrosis. × 90.

FIG. 2.

Ovum embedded in stratum compactum of endometrium: the endometrium shows the structure characteristic of the secretory phase. Spiral arteries, cut across several times in the section, are seen between two glands just to the right of the centre. × 11.

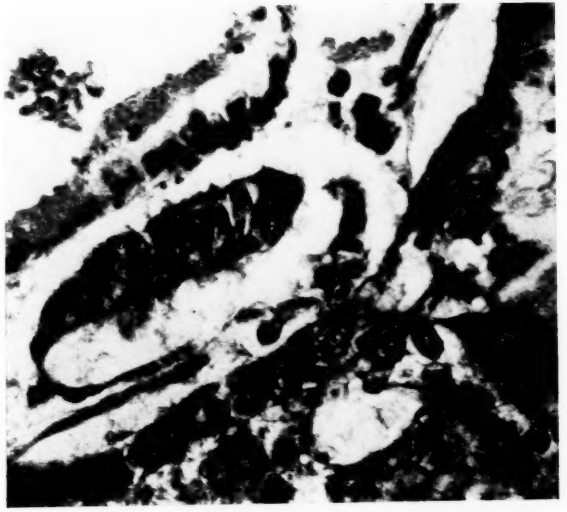

FIG. 3.

Part of ovum. The tall columnar cells of the ectodermal disc are seen to continue at the edge of the disc into the flattened cells of the amnion. The lower part (really roof) of the latter is seen to merge into the cytotrophoblast, and transition cells between the two are shown just to the right of the centre of the picture. In the upper part the cubical cells of the endodermal layer of the disc are seen to continue into the flattened cells of the exocoelomic membrane. Eosinophilic deposit is seen in the exocoelomic vesicle (above), in the amniotic cavity (below) and in the meshes of the primitive mesoblast (above and to the right). × 430.

ova, the diameter of the disc would be 0.117 mm.; that of the disc in the 11.5 day Hertig-Rock ovum is 0.138 mm. At the edge of the disc the ectodermal cells suddenly change to the flattened cells comprising the side walls and roof of the amniotic cavity, a feature which supports the views of Ramsey[5] and Heuser and Streeter[6] that in primates the ectodermal layer of the disc is formed from the inner cell mass, whereas the amnion is derived from the mesoblast, which in its turn has been delaminated from the cytotrophoblast. In the present specimen the roof of the amnion is deficient in part; here the cavity is roofed over by cytotrophoblast and transition cells between cytotrophoblast and amniotic cells are present. Definite yolk sac has not yet been formed.

Discussion and Comparison with Other Early Human Ova.

The smaller dimensions of the chorionic vesicle and of the embryonic disc, and the lesser degree of enlargement of the endometrial sinusoids in the present specimen indicate that it is younger than the 11.5 day Hertig-Rock ovum. More recently, Rock and Hertig[7] have published a preliminary report, including a photomicrograph of one section, of an implanted human ovum (Wi-8004) estimated to be 9.5 days old, but a detailed account of its structure and measurements is not given. Inspection of this photograph shows that there are many similarities with the present specimen. The 9.5 day Rock-Hertig ovum and the present specimen comprise the earliest stages of fully* implanted human ova so far discovered. The incomplete Miller ovum[8] was tentatively concluded by Streeter[9] in 1926 to have an ovulation age of 10 to 11 days. After Streeter's[10] new profile reconstruction of the Miller ovum in 1939, Hertig and Rock[3] noted that it closely resembled their 11.5 day specimen and quote Streeter as now being of the opinion that the Miller ovum is slightly older than their specimen.

Streeter[11] expressed the view that the differences in details of the form and in the rate of differentiation and growth between the embryos of man and monkey do not become appreciable until the end of the 2nd month, and that therefore for at least the 1st month or 6 weeks, the ages known for macaque embryos may be transferred to human embryos of corresponding development. The present specimen is similar in its general features to the 10-day macaque embryo described by Heuser and Streeter, but it is more advanced, however, in respect of the development of the amniotic cavity and of the primitive mesoblast. Heuser[4,12] has stressed the precocious formation of the primitive mesoblast in the monkey; the present specimen indicates that mesoblast formation in the human is even more precocious than that in the monkey, and, taken in conjunction with the human ova described by Hertig and Rock, it indicates that there are considerable differences in general organization of the human embryo between the ages of 9.5 and 12.5 days and that of macaque embryos of corresponding ages. Heuser and Streeter[6] illustrate variations in the state of development of the various elements in macaque embryos of the same age; likewise the present specimen shows some differences of detail from the 9.5-day Rock-Hertig ovum in that it is more deeply implanted, surface epithelialization has not yet occurred, the trophoblast on the abembryonic side is thicker, the exocoelomic cavity is larger and the endoderm consists for the main part of only a single layer of cells.

The exocoelomic (Heuser's) membrane, unlike that in the 11.5-day Hertig-Rock

* The term "fully implanted," as used in this paper, implies that no part of the ovum is freely exposed to the uterine cavity.

ovum, is complete and, with the endodermal disc, encloses the exocoelomic coelom. The definitive yolk sac has not yet developed. The precise method of development of the latter has not been witnessed either in the human or in the closely graded series of macaque embryos studied by Heuser and Streeter.[6] Even in the youngest human ova in which a true yolk sac may be considered to be present, namely the 13-day Torpin ovum (Krafka[13]), the 13- to 14-day Linzenmeier ovum,[14] the 13- to 14-day Yale ovum,[5] and the 13- to 14-day Peters ovum,[15] the sac is already complete. In the macaque, Heuser[4] observed that once the cells of the primitive endodermal plate begin to multiply rapidly (after the 11th day), they separate into layers to form the yolk sac, " which makes a belated appearance within a few hours," and is completely developed and segregated from the exocoelomic vesicle by the 12-day stage. As the true yolk sac has not yet developed in the 12.5-day Hertig-Rock human ovum,[3] in which the exocoelomic vesicle resembles that in the present specimen, and as the conditions in the 13- to 14-day Yale ovum resemble those in the 13-day macaque and suggest that the development of the yolk sac in the human is similar to that in the monkey, it appears that a closely graded series of human embryos round about the 12th and 13th day need to be studied in order to solve the problem of the precise manner of formation of the human yolk sac.

Of 12 early human ova described by Rock and Hertig,[7] 5 deemed to be abnormal were implanted in the anterior wall of the uterus and 7 considered to be normal were embedded in the posterior wall. These authors state that this relation may be spurious; this expectation is realized by the fact that the present specimen, which shows no abnormal features, is implanted in the anterior wall. The fact that in the present case the corpus luteum was situated in the *right* ovary would not appear to be causally related to the fact that the site of implantation of the ovum was near the entrance of the right uterine tube, in view of the findings of Rock and Hertig that in their 12 specimens the proximity of the implantation site to one or other uterine tube bore no constant relation to the ovary containing the active corpus luteum. As these authors remark, it seems that the free blastocyst is passively moved about within the uterine cavity until it is able to attach itself to the endometrium.

Following the estimation of the probable age of the ovum from its histological features, ovulation in the present instance was deduced to have occurred about the 9th day of the cycle of 28 days. In these circumstances the resultant corpus luteum would, by its progesterone (and oestrogen) secretion, begin to influence the endometrium to induce the secretory phase 5 days earlier than would have been the case if ovulation had occurred on the 14th day. It is noteworthy that the histological structure of the endometrium on the 20th day of the cycle in the present case is closely similar to that of the endometrium on the 24th or 25th day of a 28-day cycle in a number of specimens examined by the present authors, and it is certainly much more advanced in the secretory phase than many 20-day specimens examined from women with 28-day cycles; in these cases ovulation probably occurred about the 14th day. Thus, in the absence of knowledge of the ovulation time, the stage of development of the endometrium in a case of a very early pregnancy cannot be a reliable guide to the age of the embryo.

In normal circumstances there is a balanced physiological interrelation between the trophoblast and the endometrium, a normal endometrium, sensitized for the reception of an ovum by the right degree of synergic activity of progesterone and oestrogen, allowing the appropriate degree of

proliferative activity of a normal trophoblast. Alteration of any of these factors beyond a certain limit will result in a departure from this normal relationship between maternal and embryonic structures, and it is in respect of this upset of balance that early histological changes are to be sought which indicate the inability of the physiological relationship to continue and the existence of a state of affairs likely to lead to abortion. For example, the Teacher-Bryce[1] and the Möllendorff Sch.[2] ova are both surrounded by a well-marked zone of necrosis of the endometrium; consequently the belief was held for some time that implantation of the ovum was normally accomplished by necrosis of the maternal tissues. That such is not the case is indicated by the absence of necrosis of the stroma immediately adjoining the trophoblast in the present specimen as well as in others, and the necrosis in these two ova is undoubtedly to be correlated with the fact that both specimens are abortions. In the Barnes ovum (Hamilton *et al*[16]) the pathological oedema of the endometrium may be the causative factor underlying the superficial nidation of the ovum and may represent one of the very early changes in the histological structure of the endometrium which may ultimately lead to abortion. Ramsey,[5] in a specimen obtained at autopsy from a woman poisoned by an abortifacient, found that the trophoblast was devoid of cytotrophoblast and consisted solely of tightly packed plasmoditrophoblast with crowded nuclei. As Ramsey remarks, in a normal specimen a nice balance is maintained between the cytotrophoblast, plasmoditrophoblast and primitive mesoblast, and, as the last two are derived from the first, there should be an abundant supply of vigorous cytotrophoblast in the early stage of development. Such has been shown to be the case in the present specimen.

Summary.

1. The structure of a previllous human ovum estimated to be 9 to 10 days old is described. With the 9.5 day Rock-Hertig ovum, it constitutes the earliest stage of the fully implanted human ovum so far discovered.

2. The specimen indicates that primitive mesoblast formation is even more precocious in its development in the human than in other primates and that, in contrast to the claim of Streeter, differences are found in the structural details of early human and macaque ova of corresponding ages.

3. The findings favour the view that whereas the ectodermal and endodermal layers of the germ disc are derived from the formative cell mass, the amnion and exocoelomic membrane are mesoblastic in origin.

4. Comparison with other ova suggests that the yolk sac develops rapidly round about the 12th and 13th day in the human.

5. Reference is made to early pathological changes in both embryonic and endometrial elements which may lead to abortion.

6. Ovulation is deduced to have occurred about the 9th day of the cycle; the endometrium is as far advanced in the secretory phase on the 20th day in the present case as on the 24th or 25th day in a number of specimens in which ovulation probably occurred about the 14th day.

Authors' Addendum.

Since this paper was written, a more extended account of the ovum Wi–8004 has been published (Hertig, A. T. and Rock, J., *Amer. Journ. Obstet. and Gynecol.*, 1944, Vol. 47, pp. 149–184). Its authors now state that the ovum may be slightly younger than 9.5 days and that it is "approximately two-thirds implanted." This further description also shows that some of the embryonic structures are in a slightly earlier stage of development than the Davies-Harding ovum.

REFERENCES.

1. Bryce, T. H. and J. H. Teacher. "Contributions to the study of the early development of the human ovum." Glasgow, 1908, p. 7.
2. Möllendorff, W. v. *Ztschr. f. Anat. u. Entwicklungsgesch.*, 1921, lxii, 352.
3. Hertig, A. T. and J. Rock. *Contrib. Embryol. Carneg. Inst. Wash.*, 1941, xxix, No. 184, 127.
4. Heuser, C. H. *Co-operation in Research, Carneg. Inst. Wash.*, 1938, Pub. 501, p. 383.
5. Ramsey, E. M. *Contrib. Embryol. Carneg. Inst. Wash.*, 1938, xxvii, clxi, 67.
6. Heuser, C. H. and G. L. Streeter. *Contrib. Embryol. Carneg. Inst. Wash.*, 1941, xxix, No. 181, 15.
7. Rock, J. and A. T. Hertig. *Amer. Journ. Obstet. and Gynecol.*, 1942, xliv, 973. (Corrections, *Ibid*, 1943, xlv, 356.)
8. Miller, J. W. *Berl. klin. Wchnschr.*, 1913, xix, 1.
9. Streeter, G. L. *Contrib. Embryol. Carneg. Inst. Wash.*, 1926, xviii, No. 92, 31.
10. Streeter, G. L. *Anat. Rec.*, 1939, lxxii, suppl. 2, p. 75.
11. Streeter, G. L. *Annual Report Director Dept. Embryology, Carnegie Institution for* 1932-33, p. 4.
12. Heuser, C. H. *Journ. Morphol.*, 1940, lxvi, 155.
13. Krafka, J., jr. *Contrib. Embryol. Carneg. Inst. Wash.*, 1941, xxix, No. 186, 169.
14. Linzenmeier, G. *Arch. f. Gynäkol.*, 1914, cii, 1.
15. Peters, H. "Ueber die Einbettung des menschlichen Eies und das früheste bisher bekannte menschliche Placentationstadium." Leipzig and Vienna, 1899.
16. Hamilton, W. J., J. Barnes, and G. H. Dodds. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1943, l, 241.

Leukaemia and Pregnancy

BY

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LEUKAEMIA occurs rarely with pregnancy. Hofstein[1] found a total of 28 cases in the literature up to 1932. Forkner[2] in 1938 collected 53 reports. In 14 of this total, in his opinion, leukaemia had not been clearly established. Grier and Richter,[3] in 1939, collected 74 cases to which they added one report of their own. We have not found any further case records in the literature since 1939.

Patients in whom leukaemia was present prior to conception are less numerous than those occurring during pregnancy. Forkner found only 14 of his 56 patients who had leukaemia at the time of conception. Thirteen of these patients had chronic myelogenous leukaemia and one suffered from chronic lymphogenous leukaemia. The rarity of conception in myelogenous leukaemia, and still more in lymphogenous leukaemia must be ascribed in the first place to the poor condition of the subject and in the second place to the frequency of amenorrhoea. Mosler[4] found 16 cases of amenorrhoea in 21 leukaemic women. The scarcity of pregnancy in lymphogenous leukaemia of which only one case was reported, is explained by the deep modification of the uterine mucosa which the disease produces. Vignes[5] mentions lymphocytic infiltration of the uterine mucosa and nodular infiltration of lymphoid cells in the ovaries. The ovarial infiltrations are sometimes so abundant that the ovarian tissue may be completely destroyed. In myelogenous leukaemia the changes in the uterus and ovaries are less common and pregnancy is, therefore, still possible.

The reciprocal influence of leukaemia and pregnancy has been discussed by most authors who have dealt with this subject, but unanimity has not been reached. Vignes believes that spleen and liver are increased in size, that anaemia is aggravated, haemorrhages more frequent, and the number of leucocytes increased. All these symptoms should improve after delivery. Kosmak[6] states that the prognosis in a leukaemic patient is less favourable in the pregnant state. He believes that abortion or the induction of labour is indicated if leukaemia is found present. Kaplan and Connery,[7] on the other hand, found no evidence in their case that pregnancy aggravated the course of leukaemia. Forkner is in accord with this view. From the study of the reviewed cases of pregnancy in chronic myelogenous leukaemia he concludes that the accumulated data do not bear out the contention that a normal pregnancy precipitates a rapidly fatal ending or that better results are obtained by operative interference than with normal pregnancy and labour.

How is pregnancy influenced by leukaemia? Pregnancy is often interrupted before its termination. Hofstein, in 22 cases in which no abortion or artificial labour was induced found 5 premature deliveries and 4 abortions. Grier in 28 cases of chronic leukaemia complicated by pregnancy found 14 deliveries at term; 6 premature, 7 to 8½

months; 4 immature, 4½ to 7 months; 3 abortion, 4½ months or less; 1 undelivered, died.

We see from these numbers that a leukaemic patient has a good chance of carrying her pregnancy to a successful end. From Forkner's statistics one gathers the impression that pregnancy in a leukaemic patient has a better prognosis, both for mother and child, than when leukaemia appears during the gestation period.

As to the child, no leukaemic changes were ever found in the newly-born children of leukaemic mothers. Their life, as far as it is known, is not impaired by the state of the mother during gestation. We shall not discuss here cases in which pregnancy occurs during acute leukaemia nor cases in which leukaemia appears during pregnancy. These cases seem to have a far less favourable course. Neither will we discuss in this communication the problem of X-ray and radium treatment.

Report of Cases.

Case 1.

The patient, a woman, 25 years of age, married for 3 years, her husband in good health. She had one pregnancy which was terminated by a spontaneous abortion at 2½ months. There are no hereditary or familial diseases. In her past history there is only an influenza 10 years ago. The present disease started in February 1935 with a sensation of fatigue and inexplicable weariness at the slightest effort. She consulted a physician who found the spleen increased in size and made a blood count. He discovered on this occasion 400,000 leucocytes. We have not the differential count made by the physician. The patient was referred to a radiologist for treatment. She received four irradiations with X-rays, with the result that the number of leucocytes dropped to 140,000. In May 1935 the temperature rose suddenly to 40°C. and the patient was sent to a hospital in town. A blood count showed 470,000 leucocytes. It was decided, therefore, to refer the patient for treatment to our institute.

We saw the patient first on June 1st, 1935. On clinical examination the only sign of interest was an enlarged spleen reaching about 3 c.m. below the umbilical line. Enlarged lymph nodes were not found. Examination of other organs was negative. A blood count and differential count was as follows:

Red-blood corpuscles	2,300,000
White-blood corpuscles	470,000
Haemoglobin	52 per cent
Segmented neutrophiles	25 ,,
Band	20 ,,
Juvenile	9 ,,
Myeloblasts	30 ,,
Premyelocytes	4 ,,
Myelocytes	5 ,,
Metamyelocytes	1 ,,
Lymphocytes	1 ,,
Monocytes	1 ,,
Eosinophiles	3 ,,

Owing to the elevated temperature and the high myeloblast count we postponed treatment in order to study the disease for a few days. Four days later we found the number of leucocytes diminished and only 6 per cent of myeloblasts. We therefore decided to start treatment cautiously in the following manner: 40 mg. of radium were evenly distributed over the whole surface of the spleen from a distance of 3 cm., filtered by 1 Pt., and left in place for 50 hours so that a total dose of 2,000 mgh. was delivered. Blood counts were made during the 4 following days and if no untoward reaction appeared, the application of the radium was repeated. Thus we applied the radium 3 times with the result that on June 23rd, 1935, we had the following blood count:

Red-blood corpuscles	2,950,000
White-blood corpuscles	143,000
Haemoglobin	64 per cent
Segmented neutrophiles ...	42 ,,
Band	26 ,,
Juvenile	12 ,,
Myeloblasts	1 ,,
Premyelocytes	2 ,,
Myelocytes	7 ,,
Metamyelocytes	1 ,,
Lymphocytes	5 ,,
Monocytes	2 ,,
Eosinophiles	2 ,,

Treatment was then continued with X-rays. The patient received in the interval between June 26th, 1935, and July 21st, 1935, a total dose of 600 r units given on 3 splenic fields (HVL—0.95 cu.). The differential count on July 24th, 1935, was:

Red-blood corpuscles	3,540,000
White-blood corpuscles	39,000
Haemoglobin	72 per cent
Segmented neutrophiles ...	62 ,,
Band	20 ,,
Juvenile	7 ,,
Myelocytes	5 ,,
Lymphocytes	5 ,,
Monocytes	1 ,,

The spleen was reduced in size and was palpated about 5 cm. below the ribs. The general condition was improved and the temperature became normal.

During the next 1½ years the patient suffered three relapses which were treated with X-rays by the usual technique.

In February 1937 the patient returned, complaining of severe headaches, giddiness, nausea and vomiting. Her periods, which appeared always at regular intervals, had disappeared 2 months before. On physical examination the spleen was found enlarged and palpable 8 cm. below the ribs. No particulars about other organs available. The gynaecological examination revealed a pregnancy of about 2 months. Blood examination as below:

Red-blood corpuscles	3,010,000
White-blood corpuscles ...	35,000
Haemoglobin	70 per cent
Segmented neutrophiles	41 ,,
Juvenile	5 ,,
Band	28 ,,
Myelocytes	14 ,,
Myeloblasts	5 ,,
Eosinophiles	1 ,,
Basophiles	3 ,,

The general condition of the patient was good. In view of the opinion that pregnancy exerts an unfavourable influence on leukaemia and that delivery or artificial abortion brings about an improvement, it was decided to interrupt the pregnancy. Artificial abortion and curettage under general anaesthesia was made on February 2nd, 1937. The patient was discharged from the hospital in good condition. A month later she returned and complained of a sensation of tiredness and weakness. From this time onwards the blood examination showed a steady increase in the number of leucocytes, and an increase in the number of myeloblasts. In spite of irradiation a lasting improvement could not be obtained. The spleen was increasing in size, filling now two-thirds of the abdomen, and the general condition was deteriorating. The patient died in June 1937, 4 months after the abortion. Autopsy was not made.

Summarizing the main facts (see Chart I).

1. Duration of the disease 2 years and 4 months (February 1935 until June 1937).

2. Pregnancy 22 months after the appearance of the first symptoms of the disease (December 1936).

3. Death 4 months after the artificial abortion (February 1937), and 6 months after the beginning of the pregnancy.

Case 2.

A 23 year old woman was first seen on January 11th, 1938. Her chief complaint was weakness, pains in the abdomen and anorexia. No hereditary or familial diseases. The patient was the mother of a healthy child. Menstrual bleeding regular. The first symptoms of her present illness appeared in May 1937 with a feeling of a swelling in the left hypocardium. Not being inconvenienced by it the patient continued her ordinary housework. Later on a vague soreness appeared at the site of the swelling. General weakness, fatigue with the mildest exercise, and loss of appetite were noted. This general debility brought her to a physician, who sent the patient for treatment to the radium institute.

On physical examination we found a young, normally built woman, pale but well nourished; heart and lungs were normal. The spleen was greatly enlarged, extending to the inguinal region and reaching the midline of the abdomen. Liver palpable at the rib margin. Lymph nodes were not enlarged. Blood examination as follows:

Red-blood corpuscles	3,020,000
White-blood corpuscles	594,000
Haemoglobin	85 per cent
Segmented neutrophiles ...	50 ,,
Myelocytes	50 ,,
Myeloblasts	10 ,,

The patient received a course of X-ray treatment between January 18th, 1938, and February 14th,

1938. Total dose delivered was 1,400 r with 200 KV, 5 M.A. 0.5 cu. + 1 Al. S.F.D. – 40 cm. Field size 150 sq. cm. on 3 splenic fields. On February 24th, 1938, there was the following blood count:

Red-blood corpuscles	3,450,000
White-blood corpuscles	8,600
Haemoglobin	75 per cent
Segmented neutrophiles ...	75 ,,
Band	4 ,,
Myeloblasts	1 ,,
Myelocytes	5 ,,
Eosinophiles	2 ,,
Basophiles	10 ,,
Lymphocytes	3 ,,

The spleen was reduced in size and just palpable under the lower edge of the ribs.

This state was maintained with a gradual increase in the number of leucocytes until June 2nd, 1938, when we counted white-blood corpuscles, 44,000. Another series of X-rays similar to the first one, but with a total dose of 1,650 r was applied to the spleen between June 6th, 1938, and June 23rd, 1938. On July 20th, 1938, we found the number of leucocytes to be 10,600.

We did not see the patient for over a year until September 26th, 1939. On return she told a story of a normal pregnancy which ended with a normal delivery and the birth of a healthy normal boy in August 1939. At her return the patient did not complain mainly of physical weakness, but of the increasing size of her abdomen. Physical examination disclosed nothing striking except an enlarged spleen which reached the level of the iliac crest. A blood count was made which gave the following numbers:

Red-blood corpuscles	4,010,000
White-blood corpuscles ...	114,000
Haemoglobin	70 per cent
Segmented neutrophiles ...	52 ,,
Band	10 ,,
Premyelocytes	3 ,,
Myelocytes	10 ,,
Metamyelocytes	5 ,,
Myeloblasts	2 ,
Lymphocytes	2 ,,
Basophiles	4 ,,

Another series of X-rays was delivered to the spleen between September 27th, 1939, and October 10th, 1939. Total dose amounted to 500 r with 200 KV, 5 M.A.; S.F.D.—40 cm. Field size 150 sq. cm. on three splenic portals. As a result of this treatment the number of white-blood corpuscles was reduced to 43,000 and the spleen, diminished in size, was palpable under the costal edge.

The improvement lasted about 3 months. On January 7th, 1940 we saw the patient once again. There was a rise in temperature. General examination was negative excepting the spleen, which was enlarged, reaching the umbilical line. Blood count was as follows:

Red-blood corpuscles	3,900,000
White-blood corpuscles	152,000
Haemoglobin	70 per cent

with 3 per cent myeloblasts and 28 per cent myelocytes. General condition was bad and the patient was obliged to stay in bed. This time she received a combined treatment of radium and X-rays. Radium was applied on the splenic region and a dose of 1,536 mgh. was delivered to the whole surface of the spleen from a distance of 3 cm. between January 12th, 1940, and January 16th, 1940. The treatment was then continued with X-rays. 300 r were delivered in two doses of 150 r on January 10th, 1940, and January 24th, 1940.

As a result of this treatment there was an improvement in the general condition, temperature became normal and the blood count on February 4th, 1940, was as follows:

Red-blood corpuscles	4,040,000
White-blood corpuscles ...	28,000
Haemoglobin	70 per cent

In the following month the leucocyte number rose again to 125,000 An improvement was obtained by X-ray treatment on the splenic region. Higher dosage was this time required, in order to reduce the white-blood corpuscles to 42,000. The improvement lasted for an even shorter period, i.e. 2 weeks only. On March 3rd, 1940, the patient appeared with an enormous spleen filling up more than half the abdomen, large lymph nodes were apparent at the neck and the supraclavicular regions, and the skin presented a generalized eruption made up of small pustules. The white-

blood count though not very high, was 52,000. Differential count showed 52 per cent myeloblasts; 5 per cent premyelocytes; 6 per cent myelocytes and 11 per cent metamyelocytes. It was clear that it was an acute stage of the disease, which had been preceded by a period of relative radioresistance, as shown by the higher X-ray doses required to obtain a reduction of the white-blood corpuscles and the appearance of relapses at short intervals. All attempts made to obtain an improvement in the condition of the patient were useless. Transfusions, X-ray, or arsenic did not produce any improvement. The general condition worsened rapidly. During this period the leucocytes did not rise over 98,000. The last blood count gave the following result:

Red-blood corpuscles	2,430,000
White-blood corpuscles	61,000
Haemoglobin	35 per cent
Segmented neutrophiles ...	15 ,,
Band	3 ,,
Metamyelocytes	15 ,,
Myelocytes	7 ,,
Myeloblasts	41 ,,
Lymphocytes	13 ,,

The patient died of bronchopneumonia in June, 1940. Postmortem examination was not made (see chart II).

Summarizing, the following features appear to deserve emphasis:

1. Duration of the disease, 3 years, 1 month (May 1937 until June 1940).

2. Normal pregnancy starting about a year and a half (December 1938) after the appearance of the first symptoms of the disease.

3. Normal delivery 9 months later (August 1939).

4. Death of the patient 10 months after the delivery.

Discussion and Conclusions.

We have had the opportunity of following 2 cases of chronic myelogenous leukaemia which became complicated by pregnancy. Two different forms of obstetrical conduct were adopted. Table I shows the chronological data of both cases for comparison. Considering the very small number of similar cases, 13 in all, reported in the literature, we believe that the discussion of 2 new cases may be helpful in throwing some light on the problem of the reciprocal effect of leukaemia and pregnancy.

TABLE I.

	Age	Duration of leukemia at beginning of pregnancy	Gestation	Para	Normal delivery or interruption	Result Mother	Result Child	Death	Duration of disease
Case 1	25 years	22 months	1	—	Interrupted at 2 months	No ill effect	—	4 months later	26 months
Case 2	23 years	18 months	1	1	Normal delivery	No ill effect	Normal	10 months later	37 months

We wish to discuss the following aspects of this problem:

1. The influence of pregnancy on leukaemia.

2. The influence of leukaemia on pregnancy.

3. The influence of the disease on the child.

4. Is interruption of pregnancy advisable in all cases of leukaemia?

Influence of Pregnancy on Leukaemia.

No clinical or haematological aggravation was observed in Case 2 where preg-

nancy went to term. Although we did not see our patient during the period of gestation, it seems from the story she told after delivery that her condition had been excellent. We should wonder at the fact that during the whole period of pregnancy the patient did not complain of any symptoms of a relapse, though before and after these were frequent. A month after delivery the patient's general condition was still very good. Haematologically the differential count did not reveal any increased tendency towards the formation of immature leucocytes as compared to the blood before the pregnancy during a relapse. None of the dreaded complications of the disease appeared, such as an exceptional increase of the number of leucocytes and immature forms, or an abnormal increase of the size of spleen and liver. Delivery was not accompanied by unusual haemorrhages. The same holds true with Case 1. During the period of gestation this patient suffered from a relapse which in all respects had the same haematological features as her previous relapses. The course of the relapse was not modified by artificial abortion.

As to the duration of life, the patients lived 28 and 37 months respectively from the beginning of the disease. In 3 cases of leukaemia from the literature similar to case 2, the average duration of the disease was 37 months. We were not able to find data for cases like Case 1. Considering that the average duration of leukaemia in irradiated patients was found by Minot, Buckman and Isaacs[8] to be 42 months, there is no reason to assume that pregnancy curtails the patient's life. In view of the small number of cases this conclusion is, of course, tentative. As to Case 1, where the disease lasted over a period of 26 months, it may be included in the large group of leukaemic patients who die during the first 2 years of the disease. The short survival in Case 1 should not be attributed to intervening pregnancy.

Influence of Leukaemia on Pregnancy.

The statistics of Grier and Richter on pregnancy in chronic leukaemia suggest that 20 women out of 28 have a chance of a viable child and 14 women carried their pregnancy to term. In Case 1 pregnancy was interrupted after 2 months, while in Case 2 it had its normal course.

Influence of Leukaemia on the Child.

The literature shows that children born of leukaemic mothers are normal. Case 2's child was normal at the age of 2 months and 6 months.

Case 2 did not require any treatment during the period of gestation. Should this need arise, what is there to do? Great improvement may be obtained from the use of arsenic in the form of Fowler's solution and there is no contraindication to its use in pregnancy. If X-ray treatment is preferred, irradiation of the bones of the lower limbs or irradiation of the chest should be tried. In cases where an enormous spleen fills the abdomen and where methods other than direct irradiation of the spleen fail, the advisability of therapeutic abortion early in the course of gestation should be considered. If the patient is in an advanced state of leukaemia and a viable child is likely to be born, treatment may be delayed.

We may therefore conclude that pregnant leukaemic women have a good chance of a viable child and a fair one of a full term child. Their disease is not aggravated by the gestation. The child will not have leukaemia.

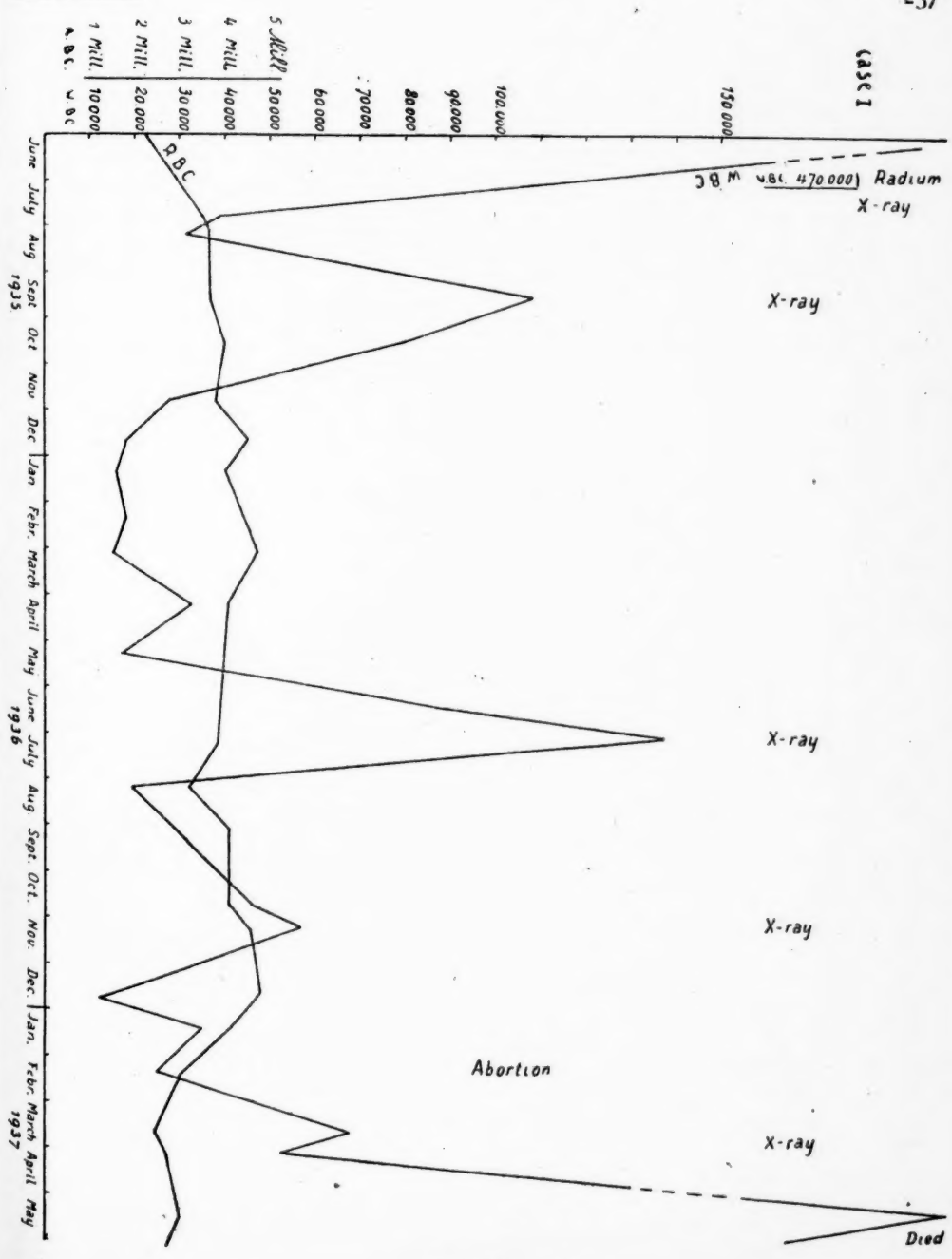
CASE I
W.B.C.
1 Mill.
2 Mill.
3 Mill.
4 Mill.
5 Mill.
R.B.C.
10 000
20 000
30 000
40 000
50 000
60 000
70 000
80 000
90 000
100 000
150 000
RBC
W.B.C. 470 000
Radium
X-ray
X-ray
X-ray
X-ray
Abortion
X-ray
Died
June July Aug Sept Oct Nov Dec Jan Febr. March April May June July Aug Sept. Oct. Nov. Dec. Jan. Febr. March April May
1935
1936
1937

CHART I.

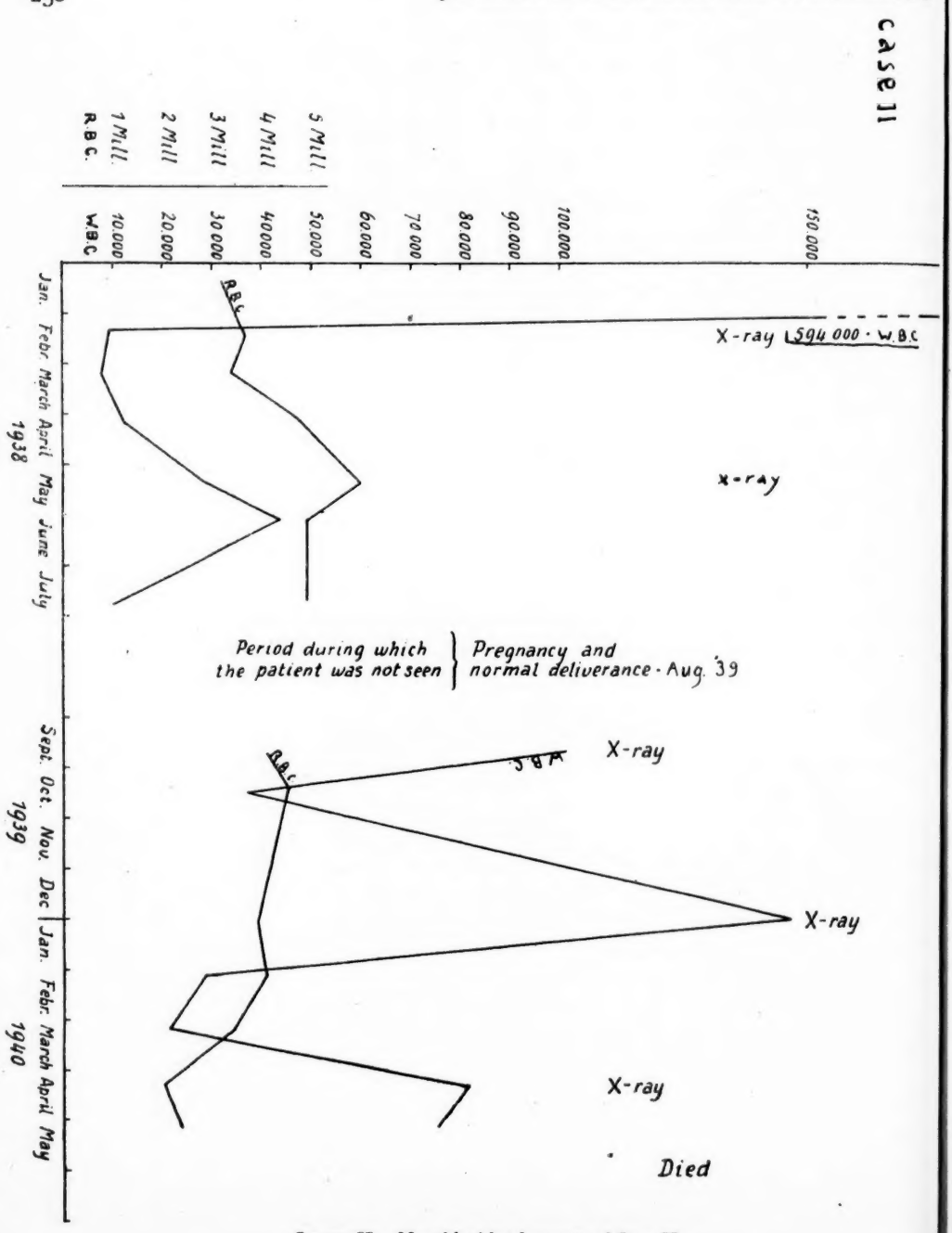

CHART II. Monthly blood counts of Case II.

SUMMARY.

1. Two cases of leukaemia complicated by pregnancy are reported. Leukaemia already existed in these cases prior to conception.

2. A pregnant leukaemic woman should be allowed to go to term as the pregnancy will neither shorten her life nor result in a leukaemic child.

REFERENCES.

1. Hofstein, J. *Gynécol. et Obstet.*, 1932, xxv, 45.
2. Forkner, C. E. "Leukemia and Allied Disorders." New York: Macmillan Co., 1938.
3. Grier, R. M., and H. A. Richter. *Amer. Journ. Obstet. and Gynecol.*, 1939, xxxvii, 412.
4. Mosler. "Die Pathologie und Therapie der Leukämie." Berlin, 1872. Cited by Vignes.
5. Vignes, H. *Presse Méd.*, 1939, xlvii, 1460.
6. Kosmak, G. W. *Amer. Journ. Obstet. and Gynecol.*, 1920, i, 485.
7. Kaplan, I. I. and J. E. Connery. *Amer. Journ. Med. Science.*, 1932, clxxxiii, 209.
8. Minot, G. R., T. E. Buckman, R. Isaacs. *Journ. Amer. Med. Assoc.*, 1924, lxxxii, 1489.

A Consideration of the White Paper "A National Health Service" in so far as it affects Maternity and Child Welfare Services

BY

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"THE Government have announced that they intend to establish a comprehensive health service for everybody in this country. They want to ensure that in the future every man and woman and child can rely on getting all the advice and treatment and care which they may need in matters of personal health; that what they get shall be the best medical and other facilities available; that their getting these shall not depend on whether they can pay for them, or on any other factor irrelevant to the real need—the real need being to bring the country's full resources to bear upon reducing ill-health and promoting good health in all its citizens."

This announcement is of particular importance as far as mothers and young children are concerned since in the past they have suffered most from lack of medical attention. They have not been covered by national health insurance and the family income is often unable to meet doctors' bills. If it is true, as is generally believed, that the future of the Nation will depend very greatly on the health, vitality and happiness of its citizens, it follows that the foundation of its health policy must be a good Maternity and Child Health service.

WHITE PAPER PROPOSALS.

It will perhaps be worth while examining the Government publication "A National Health Service" to see what it proposes in connexion with Midwifery and Child Health.

Central control is necessary to bring about and maintain a high standard throughout the country. The White Paper suggests the formation of a Central Health Services Council to express an expert view on technical aspects of the National Health Service. No doubt there will be a Maternity and Child Health Services Committee of the Central Council. Although the Central Services Council will not be elected but will be appointed by the Minister, the method could be made satisfactory to both sides, since there will be consultation with the appropriate bodies. The Minister will get the best advice from an experienced body of specialists, who are directly responsible for the lives and health of the mothers and babies and who are constantly reviewing the problems of maternal and child health in their different areas. No Minister has had this advice freely and constantly available and it pre-supposes a major reform (not envisaged in the White Paper), which would mean that the senior clinicians in any area would have the clinical supervision of the service for the area and be closely linked with the Public Health staff responsible for administration.

With regard to regional arrangements, the 'Joint Authorities' to be set up will have the responsibility of arranging for lying-in accommodation in hospital or maternity home—indeed all the institutional provision for maternity, both for normal and for complicated cases.

The ordinary functions of the Maternity and Child Welfare clinics will not be

transferred to the new Joint Authority. It is stated, however (page 39 of the White Paper), "The sufficiency of the clinics, their distribution, their connection with the necessary specialist services and the hospitals and the other main arrangements concerned will all be covered by the wider area plan." The wording of the whole paragraph on page 39 (headed Maternity and Child Welfare Services) is not very clear. It would appear that a dangerous division might arise in what should be a single service, one part under the Local Authority for general practitioners, midwives and health visitors working in the homes of the people, the health centres and the antenatal and child welfare clinics, the other under the new joint authority, consisting of the hospital and consultant and specialist services.

Existing Services.

(a) *The Maternity and Child Welfare.*

The Maternity and Child Welfare Service has developed mainly during this century, particularly in the period between the wars. The foundation of the present service was the Maternity and Child Welfare Act of 1918. The service is provided by local welfare authorities, which may be County Councils or County Borough Councils or minor authorities according to circumstances. Outside London (White Paper page 62) there are nearly 400 separate local welfare authorities. The service "is concerned to provide medical and general advice and attention (but not treatment except for a few minor ailments) to the young child and its mother, before the child's birth and afterwards until it is 5 years old or until it attends school. The service includes the provision of antenatal and postnatal clinics and welfare centres, where attendance is for the most part free and advice and minor treatment are given, the supply of milk and special foods, and the visiting and advice of health visitors at the home." . . . "For her actual confinement the expectant mother may be helped by the welfare authority—through their own provision or through arrangements made by them with other agencies—to get admission to a bed in a maternity home or hospital," . . . "or again she may and commonly does have her confinement at home and in this case there is a separately established midwifery service, which has grown up under the Midwives Acts 1902–1936 in the hands of the local supervising authorities." "Since 1936 they have been charged to see that an adequate service of domiciliary midwives is available in the area for those who need it and they do this either by arrangement with voluntary organisations or by themselves directly engaging and employing midwives." The services in Scotland are similar, with one noteworthy exception. "The Maternity Services (Scotland) Act 1937, created a domiciliary maternity service, which differs from that in England and Wales in that, while the English service is based on midwife alone, the Scottish service is based on the doctor-midwife combination. That is to say, under the Act of 1937 it is now a duty on every Local Authority in Scotland to make available to all women, who are to be confined at home and who apply for the service, the joint care throughout pregnancy, labour and the puerperium of a doctor and of a certified midwife, with the advice and help, so far as is practicable to provide it, of an expert obstetrician any time if the doctor thinks this necessary." The number of antenatal clinics run by Local Authorities has grown rapidly till in 1940 there were 1,630 in England and Wales. In 1938 61 per cent of pregnant women attended Local Authority clinics. The doctors and nurses attached to

these clinics have done much to raise the general standard of antenatal and child care and have laid the foundations of true preventive medicine, dealing as they do with life in its beginning. They have played a vital part in maintaining the health of the mother and child during the war years. In certain respects, however, results have not come up to expectation. The position as regards antenatal care was stated by Dame Janet Campbell in 1935: "Are we satisfied with the results of antenatal care so far? Most certainly not. It is true that excellent results are being obtained in selected medical or hospital practices, where the supervision is carefully organised and thoroughly carried out. Here toxaemic conditions are controlled, difficult labour anticipated, potential sources of sepsis removed, and morbidity greatly reduced. But unhappily these practices are exceptional, and there is as yet little if any appreciable effect on the maternal death-rate as a whole, or even on those pathological conditions which should, in theory, be most amenable to timely treatment"* There has been the great mistake on the part of many Local Authorities of regarding antenatal care as an end in itself, isolated from the management of labour. Pregnancy, labour and the puerperium are all parts of one continuous process and should have continuity of supervision from the same doctor or institution. The Maternity and Child Welfare officers at present appointed as assistants to the Medical Officer of Health might with advantage be replaced by two officers (1) an assistant obstetrician on the staff of the Maternity Hospital and acting as assistant to the obstetrician in charge of the Central Maternity Hospital, and (2) an assistant paediatrician on the staff of the Children's Hospital, these appointments being made on the advice of the Obstetrician, Paediatrician and Medical Officer of Health. By this means the midwifery—antenatal, intranatal and postnatal—would be under the supervision of the same person. The domiciliary midwives and health visitors should be based on the Maternity and Children's Hospitals respectively, as only in this way can a 24 hours service be maintained. The Medical Officer of Health and his staff would be the administrators and co-ordinate the work of the clinical experts.

(b) *Hospital and Specialist.*

Maternity and Children's Hospitals have grown up in a more haphazard way than the Child Welfare Services, very largely, in the first instance, as voluntary hospitals. The obstetricians attached to these hospitals comprise practically all the leading teachers of obstetrics in the country, and they have been responsible for the improvements in obstetric technique. They have little responsibility for the midwifery service outside their hospital wards, except in their own private practice and indeed, owing to the greater ease with which gynaecological practice can be organized, many, especially as they grow older and more senior, do less obstetrics and more gynaecology. In maternity hospitals more and more of the work, especially the emergency work, passes into the hands of juniors and resident members of the staff. Most of the normal or 'booked' cases, which are confined in hospital, receive their antenatal and postnatal care at the hospital outpatient clinics and the staff has therefore a wide experience of both the normal and the abnormal. Often, however, the numbers attending these clinics are too large for much time to be devoted to each case. Too little attention is paid to minor departures from normal and to the social

* *Maternity Services* (1935). Faber and Faber, London.

and economic factors. The educational function of antenatal clinics has been largely neglected. The size of the hospitals themselves has not been determined by the needs of the area but by the money available and they are invariably overcrowded. The outlook of the hospital and its staff has tended therefore to be too narrow and instead of acting as the central point of the midwifery service of the area has concentrated on internal affairs and the technical details of childbirth. This is illustrated in the annual reports of many maternity hospitals which give lists of the number of cases treated and the details of treatment. The results depend on so many factors, such as age and parity, nutrition, proportion of emergency cases, that the comparison of results from various hospitals is of limited value. It would be more valuable if the central maternity hospital in each area acted as the collecting centre for all the records for the area. Here they would be investigated and the results published in a comprehensive annual report on the midwifery service in the area in all its aspects. Probably many of the paediatricians are less well placed than the obstetricians to study the normal, since most of their work is done in children's hospitals, where they are dealing all the time with pathological processes. The appointment of paediatricians to the staffs of maternity hospitals is a great step forward, not only for the maternity hospitals but also for the paediatricians.

(c) *General Practitioner.*

The position of the general practitioners at the moment is unsatisfactory. In England the antenatal work is done under the Act by the midwife or the clinic doctor. The family doctor may be called in to treat the patient if she takes ill. He may also be called in during labour, if any abnormality develops. This is obviously unfair to the doctor. Further, since the midwife conducts most of the normal labours and since many women are now delivered in hospital, the family doctor cannot obtain a sufficiently wide experience of normal and abnormal labour to fit him to act as a consultant to the midwife. It is generally agreed that the undergraduate cannot be given sufficient practical training in obstetrics to make him a reliable obstetrician, capable of dealing with calls from experienced midwives. For the general practitioners who wish to do midwifery, special postgraduate training is necessary. In a group practice working from a health centre one or two members of the group should specialize in midwifery and take over patients from other members of the group during pregnancy and labour. The care of the patient during pregnancy and labour should not be the entire responsibility of a midwife, however well trained. The White Paper does not make clear the position of the general practitioner in relation to midwifery. In connexion with child welfare it states (page 38) "It is reasonable to look forward to the time when the general medical practitioner, the personal doctor with whom the individual and the family are regularly associated, will be able to be connected more closely with the services which are performed at special clinics, e.g. for child welfare, in which there is no doubt that in much of the general care of the young child and the handling of many of its day-to-day problems the clinics and the family doctor who have the general medical care of the child must be enabled to work in better contact for their common purpose. To make this possible on any substantial scale there will have to be more opportunity than there is now for the family doctor to acquire special experience in the children's wards of hospitals and in general child welfare subjects. . . ."

A Positive Health Policy.

(a) *General Practitioner and Health Centre.*

The criticism that the title of the White Paper " A National Health Service " is a misnomer is to some extent justified by the lack of emphasis on health in the conception of the proposed health centre schemes. These are visualized as collections of consulting rooms, simple laboratory services, nurses and typists and generally better facilities for the investigation and treatment of ill-health. This is a disappointing view. If something after the nature of the Peckham experiment had been planned, then we would have community centres where the principles of healthy living could be taught with means to hand to put them into practice. The doctors attached to such centres would have the responsibility for the health of the families attending. This would involve periodic medical overhaul with opportunities of giving practical advice on health, recreation, education and family problems. Many gynaecological complaints are due in the first place to psychological disturbances and maladjustments which could be prevented. The family doctor would have the complete care of the individual at home as well as in the centre and in health as well as in sickness. In this way the doctors, instead of being associated almost entirely with ill-health, would become family advisers and agents for positive health. That a positive health policy would be a sound investment is well illustrated by the fact that from the obstetrical point of view it can be said that if young girls were well fed and well educated in the principles of healthy living, married at a reasonably early age and had their children at the correct intervals, most of the difficulties associated with childbirth would disappear. Many social and economic factors act adversely on successful reproduction despite the most efficient maternity services. For example, the stillbirth rate at present is well over 30 per 1,000 births, yet, under optimal conditions it need not be more than 10 per 1,000.

(b) *Specialist Services.*

Just as the work of the general practitioner should be based on the health centre, the work of the obstetrician should be based on the central hospital system where the highest standard of obstetric practice must be found. He must co-operate closely with the paediatrician and with the Medical Officer of Health. In the first instance specialists would probably have to undertake most of the routine work at the health centre but gradually as certain practitioners received special training in obstetrics or child health they would take over much of the routine work and the specialists would act more as consultants. The records of all births should come to the central maternity hospital for analysis. The results should be available as a guide for shaping future policy. The value of this is seen in the organization of Dr. Bundesen in Chicago where at joint staff meetings the circumstances of every stillbirth and infant death are the subject of thorough investigation. It has led to rules for the efficient running of hospitals and nurseries being laid down, to special provision for premature babies and to arrangements for the distribution of breast milk. The reduction in the infant mortality rate in Chicago in a few years to the remarkable figure of under 30 per 1,000 live births gives some idea of what can be accomplished by an efficient organization. The obstetrician should also practice gynaecology and so have a comprehensive view of the pathological conditions of the reproductive organs in the non-pregnant as well as normal and abnormal processes of reproduction. Human reproduction is now largely planned instead of being hap-

hazard, and this planning is a necessary development of the age in which we live. The obstetrician and gynaecologist must be prepared to give advice on such subjects as sex education, preparation for marriage, contraceptives and sterility, and must know about the effects of social and economic conditions on reproduction. In addition he must also be a first-class technician, as skill in the management of the complications occurring during labour is most essential. In the past he has tended to be almost entirely a technician, but this is not now sufficient.

(c) *Outline of a Regional Scheme.*

The hospital centre should if possible be a University teaching hospital. It should have beds for antenatal, lying-in, 'clean' and 'suspect' cases with the appropriate labour room accommodation. There should be nurseries for healthy babies and a special nursery for premature babies and those with feeding difficulties. The central hospital should be built beside the general hospital, the University Medical School and the Children's Hospital. This would mean that physicians, surgeons and specialists would be available easily, as would pathologists and biochemists. Placed conveniently in the districts round the hospital there would be health centres of the type already described which would be the headquarters of the family doctors and midwives engaged in domiciliary midwifery. An obstetrician on the staff of the maternity hospital would visit each of the centres each week to see the women who had been booked to come into hospital for confinement and to see in consultation with the family doctor any case about which he wanted an opinion. In the same way a member of the staff of the Children's Hospital would supervise and direct the child welfare work in conjunction with the family doctor.

There are several advantages in decentralizing the antenatal and postnatal clinics. It would save the patient the journey to the centre; it would bring the maternity and child welfare service in close contact with the educational side of health; it would bring the general practitioners into closer contact with the specialists and provide a most valuable form of postgraduate work. It would leave the outpatient clinic at the hospital free for the investigation of special problems.

The doctors, midwives and health visitors based on the health centres would take part in the teaching of medical students and nurses. They would concentrate on the new attitude to health, that is to say, not merely the prevention of disease but the promotion of a state of positive health.

Such a scheme would take some time to develop, but in the meantime much can be done by co-ordinating the existing agencies. For example, in Aberdeen the central hospitals and medical school are grouped together. The lying-in part of the Maternity Hospital is a voluntary hospital and the antenatal and 'suspect' wards were built by the Local Authority. A liaison committee meets at regular intervals to discuss problems affecting both bodies. There is a joint staff and the Professor of Midwifery is obstetrician-in-chief of the hospital. The obstetricians staff the antenatal clinics, some of which are decentralized. The hospital district midwives are paid by the Local Authority and they work in conjunction with the municipal district midwives who share in the teaching of the pupil midwives. Where a doctor is required the family doctor booked under the scheme is called. The staff of the central hospital act as consultants under the Maternity Services Act and, in the case of whole-time members, the salaries are paid partly by the University, the Local Authority and the Voluntary Hospital. The senior Maternity and Child

Welfare Officer of the Local Authority is a member of the Maternity Hospital staff and is therefore kept in close touch with the work of the Maternity Hospital. She also lectures to medical students. The organization of the area is made easier by the fact that the Medical Officer of Health for the City is also the Medical Officer of Health for the County, and the senior Maternity and Child Welfare Officer is a regional officer. This is how one area is attempting to build up a co-ordinated regional service.

The task that lies before us is to weld the various components of the maternity and child welfare service, which have hitherto been working as separate units, into an integrated whole, in effect a comprehensive service for maternal and child health.

CRITICAL REVIEW

Oxytocic Drugs and Their Use

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ERGOT.

IN a review of drugs used to stimulate uterine contractions it is fitting to start with the oldest and still most widely used oxytocic substance. For at least four centuries, powdered ergots—the nail-like growths found on diseased rye—have been used to hasten labour that is lingering. The early use of the drug is told in Barger's *Ergot and Ergotism*, where a wealth of information will be found to charm all lovers of medical history.

The Action of Ergot. One hundred and thirty years ago Prescott described the action of ergot in labour thus:

> "The pains produced by it when a full dose is given, are very peculiarly forcing, and the contractile effort of the uterus continues to that degree, that the foetus is not suffered to retreat, but remains firmly retained where the last exacerbation of the pain left it, until it recurs again. The incessant action will continue if delivery is not effected, for an hour or more, and when it subsides, the medicine, again given, will produce the same effects. The frequency and violence of the uterine effects induced by ergot, are not more extraordinary than its almost instantaneous operation."

The remarkable properties of ergot are also its danger; and early in the history of its medical use a mounting tale of disaster to mother and foetus caused Hosack (1822) to say: "The ergot has been called *pulvis ad partum*; as regards the child, it may, with almost equal truth, be denominated the *pulvis ad mortem*." At the present day the danger of the drug is well recognized and it is no longer used during labour but is reserved for stimulation of the uterus after delivery. Ehrenberg (1940) reported the use of carefully regulated doses of ergot powder for the induction of labour. The safety of this procedure is, however, open to question.

Ergot Alkaloids. In recent years no less than 11 alkaloids and 14 alkaloidal complexes have been isolated from ergot. The alkaloids are now known to form a series of paired isomers of varying complexity (White, 1940). They are all built on a basic nucleus, lysergic acid, which, as may be guessed, itself exists in two isomeric forms. One series of isomers is laevo-rotatory to light and is pharmacologically active; the other is dextro-rotatory and is inert (Table I). Only 3 of the active alkaloids have found their way into clinical medicine: ergotoxine, ergotamine (tradenames, Femergin and Gynergen), and ergometrine. The first 2 are indistinguishable in pharmacological action. They cause uterine contractions to become frequent and powerful, but do so after a latent interval amounting to 20 minutes or more after intramuscular injection and several hours after oral administration; they therefore have little use if prompt action is required, as in cases of postpartum haemorrhage. On the other hand, ergometrine has a smaller molecule and is rapid in action, taking effect 3–4 minutes after intramuscular injection and 4–8 minutes after oral adminis-

TABLE I.

The Ergot Alkaloids (After White).

Laevorotatory (Pharmacologically active)		Dextrorotatory (Pharmacologically inactive)
Ergotoxine	($C_{35}H_{41}O_6N_5$)	Ergotinine
Ergocristine	($C_{35}H_{39}O_5N_5$)	Ψ' Ergotinine
		Ergocristinine
Ergotamine	($C_{33}H_{39}O_5N_5$)	Ergotaminine
Ergosine	($C_{30}H_{37}O_5N_5$)	Ergosinine
Ergometrine	($C_{19}H_{23}O_2N_5$)	Ergometrinine
(Based on lysergic acid)		(Based on isolysergic acid)

tration. The action lasts for upwards of an hour, after which a second dose will cause contractions to be renewed. There is little doubt that this latter alkaloid is the substance to which ergot owes its traditional clinical reputation.

Almost simultaneously with the introduction of ergometrine and the publication of its chemistry and method of extraction (Dudley and Moir, 1935), announcements were made from three other medical centres of the isolation of chemical principles having a similar clinical action (Davis *et al*, 1935; Thompson, 1935; Stoll and Burckhardt, 1935). All 4 substances were later shown to be identical. This combination of work led to useful accumulation of pharmacological knowledge but confusion was caused by the various names introduced: these matters have been fully discussed elsewhere (*Brit. Med. Journ.*, 1935). As matters now stand, ergometrine is the name by which the alkaloid is known in this country and in Europe generally, while ergonovine is the name adopted by the Council of Pharmacy of the American Medical Association. Among the trade names for the alkaloid or its salts may be mentioned Ergotrate, Ergobasin and Ergoclinine.

Dosage. The recommended dosage of ergometrine is 0.5 mg. by mouth or by intramuscular injection. For intravenous injection a dose of 0.25 mg. should not be exceeded. Some commercial firms recommend a smaller dose; thus Ergotrate is marked in ampoules of 0.2 mg.

Use in Postpartum Haemorrhage. For *prophylaxis* of postpartum haemorrhage the B.P. liquid extract of ergot m. 10–40, ergota preparata gr. 5, or a dissolved tablet of ergometrine 0.5–1.0 mg., may be given by mouth; a quicker effect is obtained by intramuscular injection of ergometrine.

For *treatment* of postpartum haemorrhage ergometrine by intramuscular or, better, intravenous injection should be used; the drug may also be given with excellent effect by direct injection into the uterine muscle (see later section).

Use in the Third Stage of Labour. The injection of ergometrine or pituitary extract into the wall of the uterus (see later section) has been recommended (Moir, 1930) as a means of shortening the 3rd stage of labour in patients in whom extensive tears are waiting to be sutured; a considerable saving of time is effected, and the surgeon no longer has to contend with periodic gushes of blood that often obscure the operation field. Davis (1940) has advised that in hospital work ergonovine (ergometrine)

should be administered as a routine by intravenous injection in a dose of 0.2 mg. as soon as the anterior shoulder of the foetus is delivered. He states that the 3rd stage of labour is thereby shortened and the blood-loss much reduced. Retention of the placenta is said to be rare and not to constitute a reasonable objection to the method. Bickers (1943) supports this practice but points out that the effect of the drug is not sufficiently lasting to prevent delayed postpartum haemorrhage; he proposes the use of mixed ergot alkaloids to secure a longer effect. To the writer it seems that the difficulty could also be overcome by an additional or repeated administration of liquid extract of ergot by mouth.

Involution of the Uterus. It has long been supposed that ergot hastens involution of the uterus. Moir and Russell (1943), after careful analysis of measurements of the uterus at different stages of the puerperium, were unable to confirm this belief. They suggested, indeed, that long-continued administration of the drug might in some circumstances be harmful.

Use in Gynaecology. The effect of ergot in checking haemorrhages from the non-pregnant uterus is doubtful. Although freely so used, the reputation of the drug in this connexion is probably an 'overflow' from its conspicuous value in the checking of postpartum haemorrhage. Ergometrine has, however, been shown to cause some increase of the contractions of the menstruating uterus and it is therefore possible that a temporary reduction of blood-flow may follow its administration.

The Gangrene-producing Effect of Ergot. It is well known that chronic ergot poisoning produces gangrene of the extremities. This effect can be reproduced experimentally by ergotoxine and ergotamine but not, it seems, by ergometrine. Many cases are on record of gangrene of the legs occurring in the puerperium; the writer has seen one patient who suffered a double amputation for gangrene starting in the 2nd week after delivery. In many of these cases ergot had been administered, sometimes in excessive doses, and was presumably the cause of the condition. In truth, however, it must be added that similar gangrene has been known to occur when ergot has not been given, and, conversely, large doses of ergot have often been given for long periods without harm. In almost all recorded cases of puerperal gangrene there has been associated sepsis; and this latter condition must be accounted the chief aetiological factor. Nevertheless, having regard to the specific action of ergot, it is clearly unwise to continue the use of the crude drug or the gangrene-producing alkaloids for more than a few days, especially if puerperal sepsis is present (Yater and Cahill, 1936; Benson, 1937; von Storch, 1938).

Posterior Pituitary Extract.

Dale (1906) found that an extract of the posterior lobe of the pituitary gland had a remarkable effect in stimulating the isolated uterus. The discovery was of immense importance. Blair Bell (1909) found that the substance had a similar effect on the human uterus during labour. Soon the extract was widely used by obstetricians; it was hoped that because it was derived from "natural" sources it would also be "physiological" in action and free from the dangers which hindered the use of ergot during labour. These hopes were badly shaken when reports of uterine rupture came to hand. A partial explanation of the occasional excessive action of the extract was forthcoming when careful methods of standardization were established. It was then found that the strength of some of the early preparations—all supposedly similar in activity—varied as much as eighty-fold

(Burn and Dale, 1922). These discrepancies were soon corrected and legal obligation was established that all posterior pituitary extracts must conform to certain oxytocic standards. The position has recently been reviewed by Dale (1942).

Use in Labour. Bourne and Burn (1927), using a method of mechanical recording, investigated the effect of small doses of posterior pituitary extract administered during labour. They formed the opinion that doses not exceeding 2 units were reasonably safe and were sufficiently active to produce a useful increase of uterine action. This recommendation has been generally accepted, although some obstetricians still maintain that the effect of pituitary extract is too unpredictable ever to allow of its safe use until the 3rd stage of labour is completed. It is right to say, however, that antagonists often speak in terms of a dosage much higher than the 2 units recommended by Bourne and Burn. These matters were the subject of a recent symposium of the American Medical Association (Pendleton, 1940; DeLee, 1940).

To some extent the use of pituitary extract in labour has followed the history of the use of ergot. In favour of pituitary extract it can be said that when the present-day standardized preparations are used in reasonable dosage, the duration of the uterine spasm (as distinct from the period of augmented contractions) is short and seldom exceeds 5 minutes; ill-effects are therefore rare. There seems to be little danger if the following conditions are strictly observed:

1. The uterine contractions must be less than average in strength and frequency.

2. There must not be any mechanical obstruction to easy delivery.

3. The condition of the foetus must be good as evidenced by a steady heart-beat and absence of meconium-stained liquor amnii.

4. The obstetrician must be at hand to give inhalations of chloroform to inhibit uterine contractions if these should become alarmingly severe.

In particular it should be emphasized that administration of the extract when the uterus is already acting briskly is highly dangerous. The price of hastening labour in those circumstances is the forfeiting of the normal margin of safety to the mother and to the foetus. As DeLee has said, "A stream-lined labour is as safe as a stream-lined parachute."

Use for Induction of Labour. Pituitary extract is often used to reinforce the "medical" induction of labour. Watson (1922) originally advocated the injection of 0.5 c.c. (5 units) or more for this purpose and claimed success in over 90 per cent of cases. These large doses are now recognized as dangerous, and it is customary to restrict the quantity to not more than $2\frac{1}{2}$ units by intramuscular injection every half hour for 6 or more doses, or until regular contractions start. The extract should not be used if the uterus is already showing signs of activity, nor repeated if the foetal heart has been slowed for more than 3 or 4 minutes by the previous injection.

Use in Postpartum Haemorrhage. Much that has been said for ergometrine can be repeated for pituitary extract. Effective contraction of a relaxed uterus can, with considerable certainty, be brought about by intramuscular injection of 5 to 10 units of pituitary extract. It is a moot point whether pituitary extract or ergometrine is better for this purpose: injection of pituitary extract carries with it a slight risk of "pituitary shock" (see later); on the other hand, there is a clinical impression that when the patient is anaesthetized, pituitary extract is more effective than ergometrine when each is given by intramuscular injection in the usual dosage.

Maximum Rapidity of Effect. When

maximum rapidity of effect is required, as in cases of severe postpartum haemorrhage, two methods of administration of oxytocic drugs stand pre-eminent. (1) Ergometrine (or, with great caution, pitocin) may be injected intravenously; the dose of the first-mentioned substance should not exceed 0.25 mg., that of the second should not exceed 2 units. (2) The same drugs may be given in twice the above dosage by direct injection into the uterine muscle. This is done by first manipulating the uterus so that it lies directly against the abdominal wall; with full antiseptic precautions the hypodermic needle is then thrust into the uterine muscle 2 inches below the umbilicus. This method has the benefit of simplicity, and by its use the most powerful uterine response is obtained. (Rawson, 1935; Moir, 1939).

Third Stage Haemorrhage. The question is often raised whether pituitary extract (or ergometrine) should be used in the treatment of bleeding *before* the expulsion of the placenta. When, in the 3rd stage of labour, the orthodox methods of controlling bleeding have failed, and especially when the Credé method of expulsion of the placenta is rendered impossible by an abnormally lax uterus, it has generally been necessary to resort to a manual removal of the placenta. This operation is not without risk—especially the introduction of sepsis—and alternative procedures are therefore worth consideration. In such cases the injection of 5 units of pituitary extract directly into the uterine wall has been advocated. Within 45 seconds the fundus will be felt to contract firmly and a Credé expression" will frequently succeed under the new conditions. Should expulsion fail, haemorrhage from the placental site will at least be checked, and ½ to 1 hour later, when the pituitary spasm is spent, the manual removal of the placenta can be undertaken in easier circumstances. Alternatively, ergometrine, 0.25 mg. by intravenous injection, can be used, but the first method is preferred (Moir, 1939).

Use in Early Pregnancy. Pituitary extract has surprisingly little effect on the uterus in early pregnancy. If, however, the uterus is already active and is aborting its contents, strong contractions can be stimulated by the injection of 10 units of the extract. For this purpose a greater effect can be obtained from the use of "normal" extract than from the purified oxytocic fraction (see later).

Use in Abdominal Hysterotomy and Caesarean Section. When in the 1st or 2nd trimester, therapeutic abortion becomes necessary, abdominal hysterotomy is often the method of choice. This operation is greatly simplified by intrauterine injection of 5–10 units of posterior pituitary extract. After the lapse of 1 or 2 minutes the uterus tightly contracts and shows a blanched and wrinkled surface. Incision, evacuation and repair can then be undertaken with almost complete absence of bleeding.

Pituitary extract or ergometrine can be similarly used during the operation of Caesarean section at term. If the incision is made in the upper uterine segment, the firm contraction caused by the pituitary extract may, however, be a disadvantage, for the sutures (which must necessarily be tied under tension) then tend to cut out. Ergometrine does not as a rule produce so intense a spasm and is therefore preferred for this purpose by some surgeons (Moir, 1936). In the case of the lower segment operation, matters are different, and the firm contraction caused by pituitary extract is an advantage. It is obvious, however, that if the latter operation is performed during labour, when the foetal head has already been thrust into the pelvic canal, injection of ecbolic drugs must be withheld until the foetus is safely extracted.

Pituitary Shock. It is well known that the injection of posterior pituitary extract will occasionally cause alarming shock. Sometimes this shock is anaphylactic (McMann, 1939; Schlayer, 1944) and probably attributable to a protein contamination in the extract. Oftener, however, it is a sudden generalized vaso-motor disturbance characterized by a peculiar ashy grey appearance of the patient (Adelman and Lennon, 1941; Sullivan and Heffernan, 1942). Besides causing contraction of the peripheral arterioles, the extract probably interferes with the coronary blood supply of the heart. There is clinical evidence that shock is more likely to occur when a second dose is given within half an hour of the first; such repetition should therefore be avoided, particularly as no useful purpose is likely to be served if the uterus has not already responded to the first injection. Pituitary shock is also said to be especially marked if the extract is given in full dose to a menstruating woman.

Posterior Pituitary Fractions (Pitressin and Pitocin). Posterior pituitary extract is now known to be capable of partial fractionation into at least two component parts. One is predominantly vasopressor, and the other predominantly oxytocic. These fractions are generally known in this country by the trade-names of Pitressin and Pitocin respectively. Despite its name it has been found that the vasopressor fraction is, in certain circumstances, also a uterine stimulant (Robson, 1933; Blair-Bell *et al.*, 1933). Excised strips of human uterine muscle obtained after lower segment Caesarean section at term have been found to respond to Pitressin in 25 times greater dilution than they do to Pitocin (Russell, 1943). The intact human uterus in the nonpregnant state, and in early pregnancy, is also more responsive to Pitressin than to Pitocin (Moir, 1934, 1944).

Despite the above qualifications there is no doubt that Pitocin is highly active on the intact human uterus at term. This substance is standardized in the usual oxytocic units, and is now widely used in obstetrics. Pitocin is, theoretically, less likely to produce pituitary shock since it is largely free from vasopressor effect. It is also to be preferred for patients suffering from pre-eclamptic toxaemia since it contains less of the antidiuretic principle which would interfere with the already abnormal water balance of these patients; and is also safer because it has less effect in raising the blood-pressure. (This latter effect is, however, seldom pronounced when ordinary doses of pituitary extract are given by intramuscular injection.) If, however, pregnancy is still in the early months, a greater response can be expected from use of "normal" extract which contains both pituitary fractions.

"Retarded" Pituitary Extract. Pituitary extract has been combined with certain inert substances with the object of retarding its activity. One such substance, known by the shortened name of pitsulphonate, has been tested clinically. The latent period after injection is found to be increased, the duration of action is lengthened, and the likelihood of tetanic contractions arising is said to be lessened (Diekmann and Kharasch, 1942).

Thymophysin. Thymophysin is a proprietary preparation in which posterior pituitary gland extract is combined with thymus gland extract. It is claimed to have the virtues of pituitary extract without some of its dangerous characters; in particular, the contractions it induces are said to be "more rhythmical." It is doubtful whether these claims have ever been substantiated, and in practice there does not appear to be any difference between the action of thymophysin and that of normal posterior

lobe pituitary extract (Roques and McLeod, 1932; Greenhill, 1932).

Quinine.

Quinine has long held reputation as an oxytocic although far less is known regarding its action in this respect than is the case with ergot or pituitary extract. Quinine does not consistently cause contraction of the isolated guinea-pig uterus until concentrations are reached that would represent a dangerously high dose in the human subject (Acton, 1921). In passing, it may be noted that, in general, quinine antagonizes the action of adrenalin; this effect has also been observed in the case of the isolated human uterus (C. S. Russell, unpublished observations). When uterine contractions are recorded during labour in the human subject, the intramuscular injection of quinine bihydrochloride is not followed by any constant or obvious effect on the contractions (Rucker, 1922; Dodek, 1932; Moir, 1934; Embrey, 1940). Nevertheless many obstetricians believe that quinine does, sometimes at least, augment contractions, and cases are even recorded in which dangerously great uterine action has followed the administration of the drug. Ganner (1935) suggests that quinine in 2 grain doses given thrice daily from the 36th week results in a shorter and easier labour. These are matters calling for further careful investigation; meantime it is safe to say that quinine, if oxytocic at all, is uncertain in its action.

Quinine has also long been used as an integral part of the well-known "medical induction" of labour. At one time it was customary to administer as much as 30 gr. in solution form, divided into 3 two-hourly doses. It is now generally believed that quinine in such large quantity is occasionally harmful to the foetus as evidenced by the passage of meconium, and cases are recorded in which foetal death has occurred some hours after the administration of the drug. For this reason the use of quinine for the induction of labour has lost much favour; those who still employ it do so in small doses only. Eastman (1938) discusses this matter and believes that quinine is safe if the total dose is kept below 10 grains. West (1938) reports an experimental study of the effect of quinine on the pregnant rabbit and concludes that the drug has a specific harmful effect on the auditory nerve of the foetus. It must be added, however, that in his experiments the drug was administered in large doses over long periods, and the conditions were therefore not comparable with those obtaining in normal obstetric practice.

Acetylcholine and Carbachol (Doryl).

The innervation of the uterus has not yet been completely elucidated. Whitehouse and Featherstone (1923) stated that sympathetic stimulation caused contraction of the circular fibres and relaxation of the longitudinal fibres of the uterine body, while parasympathetic (nervi erigenti) stimulation produced the opposite effect. There is no clear evidence that uterine contractions are directly controlled by either the sympathetic or parasympathetic nervous systems although it is probable that one or both has some modifying action. This complicated subject has been reviewed by Reynolds (1939).

Physiological research has shown that all parasympathetic stimulation is brought about by the liberation of minute quantities of a relatively simple chemical substance, acetylcholine, at the junction points between nerve and gland, or nerve and muscle. This substance is almost instantly destroyed by an esterase, so that unless stimulation is maintained the effect quickly disappears. Injection of acetycholine into the blood-stream results in a momentary

generalized parasympathetic stimulation before the substance is destroyed by the esterase. Modification of the acetylcholine molecule has produced substances that have similar properties but are more resistant to destruction. One of these synthetic products, carbachol (also known by the tradenames of Doryl and Moryl, after intramuscular injection, produces parasympathetic stimulation for 10 minutes or more. This substance is now used clinically to stimulate action of the bladder and bowel.

Single injections of acetylcholine, or of Doryl, in the usual clinical doses do not appear to cause contractions of the human puerperal uterus (Moir, 1935). It has been suggested, however, that repeated injections of acetylcholine are of service in the treatment of primary uterine inertia, for which purpose four intramuscular doses of 0.2 gm. at 4 hourly intervals are recommended (Bell and Playfair, 1937).

Oestrogens.

There is much evidence that oestrogens condition the uterine musculature and, after the lapse of 12–24 hours, render it sensitive to mechanical stimulation or to stimulation by the posterior pituitary hormone (Reynolds, 1931; Morgan, 1933; Blair-Bell *et al*, 1933; Falls and Lackner, 1936). It has been said that oestrogen enables the individual muscle fibres to contract in co-ordination (Reynolds, 1939). In pregnancy it is possible, but by no means certain, that an increasing level of blood-oestrogen causes the onset of labour. On this assumption, oestrogens in one form or other have been tried as a means of inducing labour prematurely or at term, but with disappointing results. Oestrogens have also been used as a preparation for the medical induction of labour; in particular, stilboestrol has been so used in doses as large as 150 mg. by mouth over a period of 10 hours; again the effect, if any, has been very doubtful. It is possible, however, that this premedication primes the uterus to subsequent injection of pituitary extract (Abarbanel, 1941).

Distinct from stimulation of the uterus in normal pregnancy is the stimulation of the inert uterus found in cases of missed abortion. Here, because of foetal death, the blood oestrogen has presumably fallen to a low level, and it is therefore reasonable to administer oestrogen as a preparation for stimulation of the uterus by posterior pituitary extract. Such therapy is of proved value. Jeffcoate (1940) recommended the use of oestradial benzoate 2 mg. every 8 hours for 7 or 8 days. If there was no action by the 5th day, quinine hydrochloride grs. 10 was given each hour for 3 doses, followed by injections of 5 units of pituitary extract each hour for 4 hours. Alternatively, stilboestrol 2 mg. by mouth thrice daily, or 1 mg. 4 hourly, for 7 or 8 days was used. This treatment was successful in 48 out of 55 consecutive cases.

Oestrogens have also been used to stimulate labour pains in cases of primary uterine inertia. It is obviously difficult to judge the effect of the medication since uterine contractions that have been in abeyance for many hours may spontaneously resume normal or even excessive frequency and force. Jeffcoate (1938) reported treatment of this tiresome—and dangerous—abnormality of labour by the administration of oestradial benzoate 2 mg. every hour for 8 to 10 hours. In rather more than half the observed cases he was favourably impressed with the result.

Calcium.

It is well known that the motility of isolated strips of uterine muscle is largely dependent on the composition of the fluid in which they are suspended. In particular, calcium in optimal amount is essential

(Blair-Bell *et al*, 1933). Patton and Massey (1941) reviewed the literature and reported that in uterine inertia the injection of 20 per cent calcium gluconate in amounts up to 20 c.c. was followed in 23 out of 26 cases by a slight, or, in some cases, a decided increase in frequency and strength of uterine contractions.

Lesser Known Oxytocic Drugs.

Besides the drugs already listed there are various others that are known from animal experiment to stimulate the uterine muscle, but which have not yet been assigned an assured place in therapeutics.

Gravitol is the trade-name for a synthetic substance (diethyl-amino-ethyl-ether of 2-methoxy-6-allylphenol) which is stated to have an action on the uterus like ergot. It has been used in some German clinics to augment labour pains and to treat obstetric haemorrhage. Given in a dose of 2 c.c. of 1 per cent solution by intramuscular injection it has been found to increase the frequency and power of the contractions of the puerperal uterus (Moir, 1936).

Hydrastin and hydrastinine are alkaloids obtained from *Hydrastis canadensis* (Golden Seal) which have chemical similarity to alkaloids of the opium group. Cotarnine is a related alkaloid derived from narcotine; and a similar oxidation product derived from laudanosine is marketed under the name of Lodal. These 4 alkaloids have been used in the treatment of menorrhagia and of uterine cramp. In a few experiments in non-pregnant women in which Lodal was administered by intramuscular injection in doses up to 3 grains, convincing alteration in the character of the graphically recorded uterine contractions could not be detected even during menstruation (Moir, unpublished observations).

Harmalol is an alkaloid which resembles quinine in its action on the uterus but has a better ratio between ecbolic and toxic doses. It has been tried on a small scale for its possible effect in inducing labour, and a few experiments have also been made to test its effect on the uterus during the puerperium. In doses of 1 gr. by intramuscular injection it has not produced any convincing change in the character of the contractions (Gunn, 1941).

References.

Abarbanel, A. R. *Surg., Gynecol. and Obstet.*, 1941, lxxiii, 257.

Acton, H. W. *Lancet*, 1921, i, 216.

Adelman, M. H. and B. B. Lennon. *Amer. Journ. Obstet. and Gynecol.*, 1941, xli, 652.

Barger, G. " Ergot and Ergotism," 1931, London: Gurney and Jackson.

Bell, A. C. and P. Playfair. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1937, xliv, 470.

Benson, W. T. *Edinb. Med. Journ.*, 1937, xliv, *Trans. Obstet. Soc.*, 81.

Bickers, W. *Amer. Journ. Obstet. and Gynecol.*, 1943, xlvi, 238.

Blair-Bell, W. *Brit. Med. Journ.*, 1909, ii, 1609.

Blair-Bell, W., M. M. Datnow, and T. N. A. Jeffcoate. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1933, xl, 541.

Bourne, A. and A. C. Bell. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1933, xl, 423.

Bourne, A. and J. H. Burn. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1927, xxxiv, 249.

Brit. Med. Journ. (annotation), 1935, ii, 1114.

Burn, J. H. and H. H. Dale, 1922. *Med. Res. Coun. Special Report* No. 69.

Dale, H. H. *Journ. Physiol.*, 1906, xxxiv, 163.

Dale, H. H. *Brit. Med. Journ.*, 1942, ii, 385.

Davis, M. E., F. L. Adair, G. Rogers, M. S. Kharasch, and R. R. Legault. *Amer. Journ. Obstet. and Gynecol.*, 1935, xxix, 155.

Davis, M. E. *Amer. Journ. Surg.*, 1940, xlviii, 154.

Davis, M. E. *Journ. Amer. Med. Assoc.*, 1937, cix, 1631.

Davis, M. E., F. L. Adair, and Pearl. *Journ. Amer. Med. Assoc.*, 1936, cvii, 261.

DeLee, J. B. *Journ. Amer. Med. Assoc.*, 1940, cxv, 1320.

Diekmann, W. J. and M. S. Kharasch. *Amer. Journ. Obstet. and Gynecol.*, 1942, xliv, 820.

Dodek, S. M. *Surg., Gynecol. and Obstet.*, 1932, lv, 45.

Dudley, H. W. and C. Moir. *Brit. Med. Journ.*, 1935, i, 520.

Eastman, N. J. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxv, 721.

Ehrenberg, C. J., O. F. Robbins, and J. A. Haugen. *Amer. Journ. Obstet. and Gynecol.*, 1940, xxxix, 653.

Embrey, M. P. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1940, xlvii, 371.

Falls, F. H., J. E. Lackner, and L. Krohn. *Journ. Amer. Med. Assoc.*, 1936, cvi, 271.

Ganner, P. J. *Brit. Med. Journ.*, 1935, ii, 205.

Greenhill, J. P. *Journ. Amer. Med. Assoc.*, 1932, xcviii, 1260.

Gunn, J. A. *Edinb. Med. Journ.*, 1941, xlviii, 289.

Hosack. Quoted by Barger.

Jeffcoate, T. N. A. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1938, xlv, 893.

Jeffcoate, T. N. A. *Lancet*, 1940, i, 1045.

Lackner, J. E. and A. S. Tulsky. *Journ. Clin. Endocrin.*, 1941, i, 415.

McMann, W. *Journ. Amer. Med. Assoc.*, 1939, cxiii, 1488.

Moir, C. *Edinb. Med. Journ.*, 1934, xli, *Trans. Edinb. Obstet. Soc.*, 93.

Moir, C. *Proc. Roy. Soc. Med.*, 1935, xxviii, 1654.

Moir, C. *Brit. Med. Journ.*, 1936, ii, 799.

Moir, C. *Proc. Roy. Soc. Med.*, 1939, xxxii, 928.

Moir, C. *Journ. Obstet. and Gynecol. Brit. Emp.*, 1944, li, 3.

Moir, C. and C. S. Russell. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1943, l, 94.

Morgan, T. N. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1933, xl, 1196.

Patton, G. D. and R. D. Mussey. *Amer. Journ. Obstet. and Gynecol.*, 1941, xli, 948.

Pendleton, G. F. *Journ. Amer. Med. Assoc.*, 1940, cxv, 1318.

Prescott, O. "A dissertation on the natural history and the medicinal effect of the *secale cornutum* or ergot." (1813).

Rawson, W. F. *Brit. Med. Journ.*, 1935, i, 1317.

Reynolds, S. R. M. *Amer. Journ. Physiol.*, 1931, xcvii, 706.

Reynolds, S. R. M. "Physiology of the uterus," 1939, London: Hamilton.

Robson, J. M. *Journ. of Physiol.*, 1933, lxxix, 83.

Roques, F. and D. H. Macleod. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1932, xxxix, 320.

Rucker, M. P. *Amer. Journ. Obstet. and Gynecol.*, 1922, iii, 134.

Russell, C. S. *Journ. Obstet. and Gynecol. Brit. Emp.*, 1943, l, 287.

Schleyer, E. *Brit. Med. Journ.*, 1944, i, 255.

Stoll, A. and E. Burckhardt. *Bull. Sci. Pharm.*, 1935, xlii, 257.

von Storch, T. J. C. *Journ. Amer. Med. Assoc.*, 1938, cxi, 293.

Sullivan, C. L. and R. J. Heffernan. *Amer. Journ. Obstet. and Gynecol.*, 1942, xliv, 675.

Thompson, M. R. *Science*, 1935, lxxxi, 636.

Watson, B. P. *Amer. Journ. Obstet. and Gynecol.*, 1922, iv, 603.

West, R. A. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxvi, 341.

White, A. C. *Edinb. Med. Journ.*, 1940, xlvii, 789.

Whitehouse, B. and H. Featherstone. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1923, xxx, 565.

Yater, W. M. and J. A. Cahill. *Journ. Amer. Med. Assoc.*, 1936, cvi, 1625.

ERRATUM

In the article on "Some Recent Studies and Investigations in Sterility," by Albert Sharman, which appeared in the April issue of the Journal, line 28, page 88, read "were performed with anaesthesia." This should have read "were performed *without* anaesthesia."

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

D.R.C.O.G. EXAMINATION, MARCH, 1944.

The following candidates satisfied the examiners for the DIPLOMA of the College:

Caroline Deva Baugh
Marjorie Bryan
Morag Dods
John Sterling Hogg
Edgar Gerard Housden
Douglas Latto
Mary Evelyn Long
Helen Margaret Mayer
Marjorie Lilian Penwill
James Rodney Ferrier Popplewell

The Quarterly Meeting of the Council was held on Saturday, April 29th, 1944, in the College House, with the President, Mr. Eardley Holland, in the Chair.

The Honorary Fellowship of the College was conferred on Sir Joseph Barcroft and Dr. E. Hastings Tweedy, in recognition of their services to obstetrics and gynaecology.

The following were formally admitted to the Fellowship by the President:

John Barnard Blaikley
David William Currie
James Vincent O'Sullivan
John Harold Peel
In absentia:
Harold Ian McLure
Alexander William Spain

The following were formally admitted to the Membership by the President:

Jean Rosemary Campbell Burton-Brown
Agnes Elizabeth Dorman Cathcart
Audrey Irene Freeth
David Friedlander
Matthew Macmaster Garrey
Eileen Dorothy Mary Wilson
In absentia
Anthony Pearton Bentall
John Joseph Kearney

The Annual General Meeting of the College was held on Saturday, April 29th, 1944, in the College House, with the President, Mr. Eardley Holland, in the Chair.

The following were elected to Council in place of those retiring by statutory rotation:

Representatives of the Fellows:—
John Hewitt
John Eric Stacey
James Montagu Wyatt

Representatives of the Members:—
James Bruce Dewar
John Arthur Stallworthy

The meeting was followed by the William Blair-Bell Memorial Lecture delivered by Mr. Hector R. MacLellan, M.D., F.R.F.P.S. (Glas.), M.R.C.O.G., entitled "Contracted Pelvis in Childbirth."

BOOK REVIEWS

"Atlas of Obstetric Technic." By PAUL TITUS. Illustrations by E. M. Shackleford. Price 36s. Henry Kimpton. London.

THIS book undertakes to present in pictorial form, with short titles, the subject of modern obstetric technique not accepted as standard for normal and operature deliveries as well as for various complications of pregnancy and the puerperium. It includes also a section on the technique of sterility studies.

Dr. Titus thinks of this book not only as a reference work supplementing his other book "The Management of Obstetric Difficulties" but also as fulfilling the function of teaching normal and operative obstetrics by visual means.

It is a beautifully prepared atlas of some 180 pages of illustrations, which are mostly good; the reproduction is excellent. Most of the techniques are orthodox and a wide field is covered. A few omissions are worth recording. High manual rotation of the occipito-posterior position by manipulation of the shoulders should have a place. In craniotomy of the aftercoming head, and in cleidotomy, it would have been wise to show the instrument inserted by sight under the skin of the foetus and directed from there by feel to the skull or clavicles; this reduces the risk of injury to the maternal soft tissues. The illustrations showing how, in breech presentations, to deal with extended arms, and in particular extension of the anterior arm, are not as helpful as they might be. The various techniques of rotating this arm out of its impacted position should have been illustrated more fully.

In the section on Induction of Labour, it is stated that Willet's forceps are "especially useful if infant is dead"; without doubt this instrument is useful but one wonders if the author really intends to imply that it is wise to use it in such cases to induce labour. Catheterization by a Drew-Smythe catheter to induce labour should have a place. Can the "transverse diameter between ischial spines be measured with a tongue blade?"

These criticisms cannot detract from the general excellence of this atlas, which should help to improve the technical side of obstetric practice. Those who have the responsibility of teaching will find it helpful; it should prove to be popular.

SCOTT RUSSELL

"Forsdike's Textbook Gynaecology." By J. H. PEEL. Price 21s; pp. 440. Heinemann, London.

IN revising "Forsdike's Textbook of Gynaecology," Mr. J. H. Peel has radically changed the general arrangement of the book; the whole subject matter has been expanded and in large measure rewritten, and entirely new chapters have been inserted. The majority of the original illustrations have been retained.

The arrangement of the earlier chapters is essentially orthodox. Anatomy, Embryology and Physiology are followed by a systematic discussion of disordered function, tumours, infections, and displacements. In this part the text is reasonably complete, though in no way outstanding; the wording, however, is not always as clear as might be desired, and occasionally the emphasis seems to be in the wrong direction. Thus, Fig. 59 and the text do not agree and the conservative operation of myomectomy is often only "justified" in women under 40; and it is stated that "hysterectomy is the most suitable operation for all large fibroids." With benign ovarian tumours in young persons the possibilities of resection are only to be "considered," there is no mention of the desirability of conservative surgery in such cases. More serious, the four stages of carcinoma of the cervix as described in the Atlas published by the Health Organisation of the League of Nations are incorrectly described in this book. Mr. Peel's descrip-

tion of Stage III carcinoma of cervix is " extension of the growth to the vaginal vault with infiltration of the parametrium on one side." This is very similar to the League of Nations description of a Stage II growth as " carcinoma infiltrating the parametrium on one or both sides but not invading the pelvic wall."

Apart from these scattered shortcomings, this book lends itself to serious criticism in that the illustrations are much below present-day standards. The reproduced drawings by S. A. Sewell are good; on the other hand the diagrams on the whole are poor and at times inaccurate. Where is the vagina in Fig. 195? With only one obvious exception the photo-micrographs are ill-defined and toneless and the utero-salpingograms are not convincing. There is also unnecessary repetition; for example, there are three very similar reproductions of dermoids cysts of the ovary, two of xanthofibroma theca cellulare, three separate diagrams of uterine fibroids and two of papilliferous ovarian cystadenomata both showing substantially the same features. A sense of proportion is not always present. There are three reproductions illustrating a method of repairing vesico-vaginal fistula yet only two of myomectomy, which incidentally show a poorly placed incision. There is no illustration of the removal or enucleation of an ovarian cyst.

The chapters dealing with sterility, contraception, and gynaecological symptomatology and treatment including pre-operative and post-operative management are superior to the first part and it is here that the main value of the book is to be found. The emphasis laid on the psychological aspect of disease is praiseworthy, though the statement that " pain is never imaginary though it is commonly exaggerated " seems dangerous without the additional explanation that it may be the presenting symptom in patients suffering from one of the " neuroses."

SCOTT RUSSELL

" Clinical Roentgenology of Pregnancy." By WILLIAM SNOW, M.D. Published by Charles C. Thomas, Springfield, Illinois, Baltimore, Maryland, 1942.

THIS comprehensive manual by an acknowledged expert brings to a focus the need for recognition of the high value of X-ray diagnosis in the field of obstetrics. Progress in this direction has been retarded by technical difficulties, and their removal has served to bring the scope of X-rays in midwifery up to the standard achieved in other spheres, such as those of the gastro-intestinal, respiratory and urinary tracts.

The author has stated his object is not only to guide the obstetrician in the use of diagnostic X-rays, but to offer him a method or methods simple enough for him to employ himself. The reviewer feels that the obstetrician of to-day should turn to the radiologist for guidance and co-operation, but should not attempt to carry out the actual radiography. The technical details set out so lucidly in this book should prove instructive to the radiologist, but surely the obstetrician, already overburdened with work, can hardly have time to do more than be grateful for the knowledge imparted from an interpretation of the findings. Correlation of clinical and radiological data is, of course, essential, and it is hoped that all future maternity hospitals will have incorporated in their buildings a fully equipped X-ray department. This book, in spite of this too ambitious object, is an excellent treatise that will repay perusal, and it deserves a place in the library of all concerned with practical obstetrics.

O. LLOYD

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as war conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W.12.

	REF.
ANATOMY	1
PHYSIOLOGY	4
PREGNANCY	
General	28
Normal	
Antenatal care	30
Nutrition	34
Abnormal	
Toxaemias	39
Abortion	42
Association with disturbances of other maternal systems	46
Association with infectious diseases	59
Ectopic pregnancy	64
Miscellaneous	68
LABOUR	
Normal	69
Anaesthetics, analgesics	73
Abnormal	83
PUERPERIUM	
Normal	
Lactation	90
Abnormal	
Infections	92
THE INFANT	
General	94
Infections	102
Congenital defects	112
Blood	124
Nutrition	137
Welfare	145
Mortality	149

INDEX TO CURRENT LITERATURE 261

REF.

MATERNAL WELFARE 161

MATERNAL MORTALITY 162

OBSTETRIC OPERATIONS 163

MISCELLANEOUS 169

GYNAECOLOGY

General 173
Disorders of function
Menstrual disorders 175
Menopause 182
Dyspareunia 183
Sterility 184
Abnormalities of the reproductive organs 190
Infections of the reproductive organs 193
New growths of the reproductive organs 198
Gynaecological operations 220
Miscellaneous 225

BOOKS

ANATOMY

1. "Submuscle pelvic tissue spaces. Anatomy and clinical considerations." B. H. Brunkow. *Amer. Journ. Surg.*, January 1944, LXIII, 86–9.

2. "The obliquely ovate or Naegele pelvis. A commentary and report of four cases." H Thoms. *Journ. Amer. Med. Assoc.*, January 29th, 1944, CXXIV, 294–6.

3. "The development of the periurethral glands in the human female." J. W. Huffman. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 773–85.

PHYSIOLOGY

4. "The constitutional type of female precocious puberty with a report of 9 cases." E. Novak. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 20–42.

5. "Effects of low atmospheric pressures on the activity of the thyroid, reproductive system, and anterior lobe of the pituitary in the rat." A. S. Gordon, F. J. Tornetta, S. A. D'Angelo and H. A. Charipper. *Endocrinology*, December 1943, XXXIII, 366–83.

6. "Effect on spermatozoa of tissue fluids encountered in the female reproductive tract." R. L. Brown. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 873–6.

7. "Reproductive system of pregnant hermaphrodite rabbit." E. M. Sheppard, *Journ. Anat.*, 1943, LXXVII, 288–93. (*Brit. Chem. Physiol. Abstr.*, A III, January 1944, 30.)

8. "Plasma vitamin C levels in women during the menstrual cycle." O. Mickelsen, A. L. Dippel and R. L. Todd. *Journ. Clin. Endocrinol.*, November 1943, III, 600–2.

9. "The effect of medical diathermy on the menstrual cycle of the monkey (Macacus Rhesus)." H. A. Strauss, L. Fisher and B. B. Rubenstein. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 861–6.

10. "The validity of 'ovulation potentials.'" J. M. Snodgrass, J. Rock and M. F. Menkin. *Amer. Journ. Physiol.*, December 1943, CXL, 394–415.

11. "Detecting the exact time of ovulation by ovulation potentials." Editorial. *Journ. Amer. Med. Assoc.*, January 29th, 1944, CXXIV, 298–9.

12. "Prolongation of pseudocyesis by induction of deciduomata in the rat." B. H. Ershoff and H. J. Deuel, jr. *Proc. Soc. Exp. Biol. and Med.*, November 1943, LIV, 167–8.

13. "Relaxation of the pelvic ligaments of castrate hysterectomized guinea pigs induced by progesterone." N. W. Fugo. *Proc. Soc. Exp. Biol. and Med.*, November 1943, LIV, 200–1.

14. "Absorption of radioactive sodium instilled into the vagina." W. T. Pommerenke and P. F. Hahn. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 853–5.

15. "Observations on the fluorescence, birefringence and histo-chemistry of the rat ovary during the reproductive cycle." E. W. Dempsey and D. L. Bassett. *Endocrinology*, December 1943, XXXIII, 384–401.

16. "Oestrogens and the ovary." Editorial. *Brit. Med. Journ.*, February 19th, 1944, I, 261.

17. "Reproductive capacity of adult female rats treated prepuberally with oestrogenic hormone." J. G. Wilson. *Anat. Rec.*, 1943, LXXXVI, 341–63. (*Brit. Chem. Physiol. Abstr.*, A III, February 1944, 110.)

18. "Action of testosterone and prolactin on the corpora lutea of the rat." C. F. Fluhmann and G. L. Laqueur. *Proc. Soc. Exp. Biol. and Med.*, November 1943, LIV, 223–5.

19. "The metabolism of estrone in surviving rabbit, bovine and human endometrium." C. M. Szego and L. T. Samuels. *Journ. Biol. Chem.*, December 1943, CLI, 599–605.

20. "Contribucion al estudio de la motilidad uterina humana 'in vivo.'" (Motility of the human uterus 'in vivo.') R. Percorone. *Rev. Med. Rosario*, 1943, XXXIII, 409. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 39.)

21. "Relation of number of injections to the titer of sperm iso-agglutinins in mice." G. D. Snell and H. Poucher. *Proc. Soc. Exp. Biol. and Med.*, November 1943, LIV, 261–3.

22. "Concentration of human iso-agglutinins in various conditions." L. Bardeci. *Rev. Soc. Argentina Biol.*, 1942, XVIII, 467–71. (*Biol. Abstr.*, January 1944, XVIII, 126.)

23. "Levine's hypothesis of maternal iso-immunization" (letter). L. Hogben. *Nature*, February 19th, 1944, CLIII, 222–3.

24. "The comparative value of endometrial biopsies and vaginal smears." T. Neustaedter and L. L. Mackenzie. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 81–92.

25. "Vitamin E deficiency in the rat. V. Uterine changes in chronic deficiency." M. M. O. Barrie Sweeten. *Biochem. Journ.*, 1943, XXXVII, 523–5.

26. "Diffuse calcification of the placenta demonstrable *in vivo*." S. Thomas. *Radiology*, December 1943, XLI, 573–5.

27. "Induction of decidua-placental hemorrhage in mice by the endotoxins of certain gram-negative bacteria." P. A. Zahl and C. Bjerknes. *Proc. Soc. Exp. Biol. and Med.*, December 1943, LIV, 329–32.

PREGNANCY

General

28. "The use and abuses of the female sex hormones." T. N. MacGregor. *Edinb. Med. Journ.*, January 1944, LI, 39–56.

29. "Endocrine therapy in gynaecology and obstetrics." Critical review. P. M. F. Bishop. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 51–63.

Normal

Antenatal care

30. "A study of antenatal and postnatal care in England, and suggested measures for an organized maternal welfare service in post war Czechoslovakia." W. Spitzer. *Bull. Czech. Med. Assoc. in Gt. Britain*, December 1943, II, 16–26.

31. "Comparative value of Roentgen versus clinical methods of pelvic examination in obstetrics: roentgenologic aspects." S. G. Henderson. *Pennsylvania Med. Journ.*, June 1943, XLVI, 902–6. (*Radiology*, January 1944, XLII, 101.)

32. "Comparative value of Roentgen versus clinical methods of pelvic examination in obstetrics: clinical aspects." H. A. Power. *Pennsylvania Med. Journ.*, June 1943, XLVI, 907–9. (*Radiology*, January 1944, XLII, 102.)

33. "Chest screening in the antenatal clinic." R. Frank and A. L. Jacobs. *Brit. Med. Journ.*, March 18th, 1944, I, 394.

Nutrition

34. "Nutrition surveys carried out in Scotland." V. P. Sydenstricker. *Health Bull.* (Dept. Health, Scotland), April 1943, II, 43–5. (*Bull. Hygiene*, February 1944, XIX, 137.)

35. "Vitamin status of the population of the west coast of Newfoundland with emphasis on vitamin C." E. McDevitt, M. A. Dove, R. F. Dove and I. S. Wright. *Ann. Int. Med.*, January 1944, XX, 1–11.

36. "Nutrition studies during pregnancy. IV. Relation of protein content of mother's diet during pregnancy to birth length, birth weight and condition of infant at birth." B. S. Burke, V. V. Harding and H. C. Stuart. *Journ. Pediatr.*, November 1943, XXIII, 506–15.

37. "Supplementary feeding in pregnancy." M. I. Balfour. *Lancet*, February 12th, 1944, I, 208–11.

38. "Gum tumours in pregnancy and gingivitis gravidarum" (probably due to vitamin C deficiency). W. G. Cross. *Brit. Dental Journ.*, 1943, LXXV, 85–9. (*Nutr. Abstr. Rev.*, January 1944, XIII, 460.)

ABNORMAL

Toxaemias

39. "Intravenous amino acids in nephrotic toxemia of pregnancy." J. E. Corr, W. Wagner and M. Hetzer. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 70–80.

40. "The placenta in eclampsia and nephritic toxaemia." N. M. Falkiner and J. O. E. Apthorp. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 30–37.

41. "Toxaemia of pregnancy and the hypertensive states." Editorial Review. *Brit. Med. Journ.*, March 18th, 1944, I, 398–9.

Abortion

42. "Indagine sulla frequenza dell'aborto umano da Brucellosi in provincia du Brescia." (Frequency of abortion due to brucellosis in Brescia.) G. Mussi. *An. Ostet. e Ginec.*, August 1942, 665–81. (*Med. Española*, November 1943, X, 759.)

43. "Therapeutic abortion by X rays." C. E. Garciga. *Rev. Med. Cubana*, March 1943, LIV, 270–80. (*Radiology*, January 1944, XLII, 104.)

44. "Therapeutic abortion in Switzerland." Editorial review. *Brit. Med. Journ.*, March 11th, 1944, I, 367.

45. "Prenatal mortality and the birth rate." A. S. Parkes. *Nature*, February 26th, 1944, CLIII, 245–6.

Association with disturbances of other maternal systems

46. "Abdomen agudo y embarazo." (Acute abdomen and pregnancy.) M. G. Portela. *Toko-Ginec. Pract.* (Madrid), December 1943, II, 332–42.

47. "Strangulated uterus in inguinal hernia (in early pregnancy)." R. Laird. *Proc. Roy. Soc. Med.*, January 1944, XXXVII, 86.

48. "Treatment of uncontrollable vomiting of pregnancy." J. Bazan and R. Dubrovsky. *Semana Med.*, January 28th, 1943, I, 221. (*Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 909.)

49. "Tratamiento de la hiperemesis gravidica con el sulfato de magnesio." (Treatment of hyperemesis of pregnancy with magnesium sulphate.) O. G. Rossi. *Bol. Soc. Med. Antofagasta*, September 2nd, 1943; *Rev. Med. Chile*, October 1943, LXXI, 1020.

50. "La médula ósea en la hiperemesis gravidarum." (The bone marrow in hyperemesis gravidarum.) J. F. Bover and L. A. Colomer. *Med. Espan.*, November 1943, X, 679–82.

51. "The influence of hormones upon varicose veins in pregnancy." A. M. McCausland. *West. Journ. Surg.*, May 1943, LI, 199–200. (*Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 905.)

52. "The ultimate effect of pregnancy on rheumatic heart disease." N. H. Boyer and A. S. Nadas. *Ann. Int. Med.*, January 1944, XX, 99–107.

53. "Conjugated estrogens in human pregnancy serum." A. E. Rakoff, K. E. Paschkis and A. Cantarow. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 856–60.

54. "Studies on the Rh factor." H. A. Schwartz and P. Levine. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 827–35.

55. "Pregnancy associated with congenital cystic disease of the lung." J. Preston Maxwell. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 42–3.

56. "An analysis of 388 cases of rheumatoid arthritis." J. G. Sclater. *Ann. Rheumatic Dis.*, December 1943, III, 195–206.

57. "The pituitary antidiuretic hormone in diabetes insipidus: 8 cases of diabetes insipidus, 4 with pregnancy." F. E. Harding. *West. Journ. Surg.*, 1943, LI, 269. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 99.)

58. "Fetal and neonatal mortality in pregnancies complicated by diabetes mellitus." H. C. Miller, D. Hurwitz and K. Kuder. *Journ. Amer. Med. Assoc.*, January 29th, 1944, CXXIV, 271–5.

Association with infectious diseases

59. "Epidemic encephalitis and pregnancy." A. J. Hall. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 49–50.

60. "Report of a select committee on health services in Northern Ireland." (Tuberculosis and maternity services.) Belfast: H.M.S.O., 1944: (*Brit. Med. Journ.*, February 19th, 1944, I, Suppl. 28).

61. "The harmful influence of pregnancy on advanced tuberculosis as modified by collapse therapy." J. W. Cutler. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 1–19.

62. "The effect of pregnancy and parturition on pulmonary tuberculosis" (letter). R. C. Cohen. *Brit. Med. Journ.*, February 5th, 1944, I, 196.

63. "Rubella and congenital malformations." (Annotation.) *Lancet*, March 4th, 1944, I, 316.

Ectopic pregnancy

64. "Coexisting intrauterine and extrauterine pregnancies. A review with the report of a case." S. J. King. *New Engl. Journ. Med.*, December 23rd, 1943, CCXXIX, 965–70.

65. "A combined extrauterine and intrauterine pregnancy." W. E. Studdiford and G. Speck. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 118–21.

66. "Abdominal pregnancy requiring secondary removal of the placenta." J. W. Pearson and J. Parks. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 127–9.

67. "Abdominal pregnancy, fifth month." L. E. Phaneuf and H. E. MacMahon. *Amer. Journ. Surg.*, January 1944, LXIII, 107–17.

MISCELLANEOUS

68. "Intravenous pyelograms in normal and abnormal pregnancies." D. C. Leary and J. P. Peters. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 803–9.

LABOUR

NORMAL

69. "The blood pressure in midwifery." W. Radcliffe. *Brit. Med. Journ.*, March 11th, 1944, I, 354–8.

70. "The care of the parturient woman in relation to neonatal mortality." E. C. Sage. *Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 339–43.

71. "The care of the fetus during labor." R. Torpin. *Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 343–51.

72. "Sinergia de los movimientos de extension o flexion con el de rotacion en el descenso del ovoide cefalico." (Mechanism of extension and flexion during rotation and descent of the foetal head.) J. M. M. Porcar. *Toko-Ginec. Pract.* (Madrid), December 1943, II, 351–2.

Anaesthetics, analgesics

73. "La anestesia en obstetricia." (Anaesthesia in obstetrics.) M. Ruiz. *Rev. Obstet. y Ginec.* (Venezuela), 1943, III, 79–93.

74. "Elective painless rapid childbirth anticipating labour." H. Koster and L. Perrotta. *Exp. Med. and Surg.*, 1943, I, 143–7. (*Brit. Chem. Physiol. Abstr.*, A III, January 1944, 58.)

75. "Our experiences with the Hingson-Edwards technique of continuous caudal analgesia." J. S. Chaikoff. *Canad. Med. Assoc. Journ.*, January 1944, L, 52–60.

76. "Continuous caudal anesthesia in 200 obstetric patients." H. Lyons and F. M. Hansen. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 105–10.

77. "Spinal anesthesia for Cesarean section." F. Weintraub and M. S. Merriam. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 836–40.

78. "Cesarean section under continuous caudal analgesia. A preliminary report." C. B. Lull and J. C. Ullery. *Journ. Amer. Med. Assoc.*, January 8th, 1944, CXXIV, 90–3.

79. "Pethidine as an obstetric analgesic. A report on 150 cases." B. Gallen and F. Prescott. *Brit. Med. Journ.*, February 5th, 1944, I, 176–9.

80. "Obstetric analgesia with pethidine." W. Spitzer. *Brit. Med. Journ.*, February 5th, 1944, I, 179–81.

81. "Heroin and pethidine during labour" (letter). M. Venters. *Brit. Med. Journ.*, March 4th, 1944, I, 339.

82. "Demerol (S-140) and scopolamine in labor. A study of 1,000 cases." W. R. Schumann. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 93–104.

ABNORMAL

83. "Vagitus uterinus." G. H. Ryder. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 867–72.

84. "The uterine contractions associated with prolonged labors. Observations of uterine motility made with the Lorand tocograph." D. P. Murphy. *Surg., Gynecol and Obstet.*, February 1944, LXXVIII, 207–10.

85. "Midwifery in the Transkei, with particular reference to vesico-vaginal fistulae." J. D. Joubert. *S. Afr. Med. Journ.*, January 22nd, 1944, XVIII, 19–20.

86. "Induction of labour in contracted pelvis by digital separation of the membranes" (letter). D. Chalmers Wiseman. *Brit. Med. Journ.*, February 12th, 1944, I, 221.

87. "Induction of labour by separation of membranes" (letter). W. Calvert. *Brit. Med. Journ.*, March 4th, 1944, I, 339.

88. "Results of external prophylactic version." M. V. Trubkowitch and B. A. Archangelsky. *Brit. Med. Journ.*, February 12th, 1944, I, 220.

89. "Obstetric 'shock'" (letters). N. Alders. *Brit. Med. Journ.*, February 5th, 1944, 197; M. Reddington, February 19th, 1944, I, 264.

PUERPERIUM

NORMAL

Lactation

90. "Observaciones clinicas sobre el empleo de estrogenos por via bucal para la interrupcion de la lactancia." (Clinical observations on the oral administration of oestrogens for the interruption of lactation.) Romero-Girón. *Soc. Ginec. Españ: Toko-Ginec. Pract.* (Madrid), December, 1943, II, xiii–xiv.

91. "Mastitis obliterans." R. L. Payne, A. F. Strauss and R. D. Glasser. *Surgery*, November 1943, XIV, 719–27.

ABNORMAL

Infections

92. "Profilaxis de la infeccion puerperal" (Treatment of puerperal infection.) R. H. Liria. *Toko-Ginec. Pract.* (Madrid), December 1943, II, 343–50.

93. "Penicillin. Case report of a patient who recovered from puerperal sepsis hemolytic streptococcus septicemia." R. McN. Mitchell and S. Kaminester. *Amer. Journ. Surg.*, January 1944, LXIII, 136–40.

THE INFANT

GENERAL

94. "Intelligence and season of conception." J. A. Fraser Roberts. *Brit. Med. Journ.*, March 4th, 1944, I, 320–2.

95. "Sex ratio" (letter). H. de Peyer. *Lancet*, March 18th, 1944, I, 390.

96. "Untersuchungen über die Gewichtsverhältnisse der Neugeborenen auf Grund des 40 jährigen Materials der Klinik." (Studies on the weight of newborn infants based on clinical material obtained over a period of 40 years.) I. Korompai. *Zts. Geburtsh. Gynäk.*, 1942, CXXIV, 36. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 45.

97. "Folds and creases of the skin during childhood." E. Nassau. *Amer. Journ. Dis. Childr.*, December 1943, LXVI, 615–23.

98. "Liver function in the newborn infant." G. W. Salmon and E. E. Richman. *Journ. Pediatr.*, November 1943, XXIII, 522–33.

99. "Subdural hematoma in infancy." F. D. Ingraham and D. D. Matson. *Journ. Pediatr.*, January 1944, XXIV, 1–37.

100. "An enquiry into the causation and characteristics of cephalhaematomata." J. B. Hartley and C. W. F. Burnett. *Brit. Journ. Radiol.*, February 1944, XVII, 33–41.

101. "Blood or plasma transfusion in infants: a new route." R. F. Pinto. *Rev. Soc. Pediatr. Rosario*, May/August 1943, VIII, 108. (*Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 395.)

See also Ref. 36.

INFECTIONS

102. "Epidemic diarrhea of the newborn: report of two outbreaks." P. A. Lembcke, J. J. Quinlivan and N. G. Orchard. *Amer. Journ. Publ. Health*, October 1943, XXXIII, 1263. (*Journ. Amer. Med. Assoc.*, December 25th, 1943, CXXIII, 1139.)

103. "Treatment of epidemic diarrheas and dysenteries in infants and young children. Comparative study of different treatments and their results." K. Glaser and J. W. Bruce. *Journ. Pediatr.*, January 1944, XXIV, 53–61.

104. "Acquired syphilis in infants and in children. Report of 3 cases." G. W. Cresswell, E. Seech and W. L. Murray. *Amer. Journ. Dis. Childr.*, December 1943, LXVI, 611–14.

105. "Intestinal thrush. A report of two cases in young infants." A. R. Macgregor and J. L. Henderson. *Arch. Dis. Childh.*, December 1943, XVIII, 186–7.

106. "Mastoiditis in infants" (letter). P. W. Leathart. *Brit. Med. Journ.*, February 5th, 1944, I, 197.

107. "A case of poliomyelitis in a newborn infant." A. H. Biermann and E. A. Piszczek. *Journ. Amer. Med. Assoc.*, January 29th, 1944, CXXIV, 296–7.

108. "Bullous impetigo (pemphigus) neonatorum." B. R. Nisbet. *Med. Officer*, October 23rd, 1943, LXX, 133–4. (*Bull. Hyg.*, January 1944, XIX, 2.)

109. "New law regarding prophylactic treatment of eyes of infants." Massachusetts Department of Public Health. *New Engl. Journ. Med.*, January 20th, 1944, CCXXX, 93.

110. "The incidence and treatment of ophthalmia neonatorum (with discussion)." A. Sorsby. *Proc. Roy. Soc. Med.*, February 1944, XXXVII, 162–3.

111. "The sulphonamides in ophthalmia neonatorum." A. Sorsby and E. L. Hoffa. *Brit. Med. Journ.*, March 11th, 1944, I, 353–4.

CONGENITAL DEFECTS

112. "Jaundice and conditions associated with this phenomenon." M. Fallon. *Journ. Pediatr.*, December 1943, XXIII, 721–37.

113. "Exomphalos" (letter). E. W. Thomas. *Brit. Med. Journ.*, March 25th, 1944, I, 435

114. "Study of a case of external (extracranial) hydrocephalus." J. A. Peschard. *Gac. Med. Mexico*, 1943, LXXIII, 35. (*Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 907.)

115. "The occurrence of anencephalic monsters in successive pregnancies." J. K. Quigley. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 879–80.

116. "Transection of the spinal cord due to injury at birth." M. Horan. *Arch. Dis. Childh.*, December 1943, XVIII, 188–9.

117. "Spina bifida and its associated skull defects." J. B. Hartley and C. W. F. Burnett. *Arch. Dis. Childh.*, December 1943, XVIII, 173–7.

118. "Prolapsus uteri associated with spina bifida and clubfoot in newborn infants." R. Torpon and C. M. Burpee. *Amer. Journ. Dis. Childr.*, December 1943, LXVI, 627–8.

119. "Two congenital deformities of the tibia: congenital angulation and congenital pseudarthrosis." E. R. Williams. *Brit. Journ. Radiol.*, December 1943, XVI, 371–6.

120. "The etiology of congenital cerebral palsy. A statistical and clinical study." H. Yannet. *Journ. Pediatr.*, January 1944, XXIV, 38–45.

121. "Congenital complete heart block." J. Thomson. *Arch. Dis. Childh.*, December 1943, XVIII, 190–3.

122. "Two cases of imperforate anus." I. A. J. McCready. *Brit. Med. Journ.*, February 26th, 1944, I, 290.

123. "Pyloric stenosis in identical twins" (letter). F. L. King Lewis. *Brit. Med. Journ.*, February 12th, 1944, I, 221.

See also Ref. 63.

BLOOD

124. "Physiology of the hematopoietic system in infants and young children, including the blood picture at birth and in young infants." P. Lee. *Journ. Pediatr.*, December 1943, XXIII, 676–9.

125. "Diseases of blood in infants and young children including the hemorrhagic states." H. G. Poncher. *Journ. Pediatr.*, December 1943, XXIII, 680–90.

126. "The deficiency and dyshematopoietic anemias of infancy and childhood." R. R. Kracke and W. R. Platt. *Journ. Pediatr.*, December 1943, XXIII, 691–713.

127. "Erythroblastosis of the icterus gravis type. Report of two cases with recovery." D. A. Nickerson and R. T. Moulton. *New Engl. Journ. Med.*, December 2nd, 1943, CCXXIX, 863–7.

128. "The pathogenesis of erythroblastosis fetalis. A review." P. Levine. *Journ. Pediatr.*, December 1943, XXIII, 656–75.

129. "Nucleated erythrocytes in newly born infants in relation to maternal Rh compatibility." A. E. Casey and S. H. Crowson. *Proc. Soc. Exp. Biol. and Med.*, December 1943, LIV, 320–2.

130. "The survival of transfused erythrocytes in haemolytic disease of the newborn." P. L. Mollison. *Arch. Dis. Childh.*, December 1943, XVIII, 161–72.

131. "Erythroblastosis neonatorum." M. M. de Mendizabal, E. de Amilibia and J. S. Harguindey. *Rev. Clin. Espan.*, June 30th, 1943, IX, 366. (*Journ. Amer. Med. Assoc.*, January 29th, 1944, CXXIV, 327.)

132. "The incidence of haemolytic disease of the foetus ('erythroblastosis foetalis') in different families. The value of serological tests in diagnosis and prognosis." K. E. Boorman, B. E. Dodd and P. L. Mollison. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 1–23.

133. "Rhesus antibody in Rh-positive mother causing haemolytic disease of newborn." A. J. McCall, R. R. Race and G. L. Taylor. *Lancet*, February 12th, 1944, I, 214–5.

134. "Eugenic and genetic aspects of the Rh factor." Editorial. *Brit. Med. Journ.*, February 19th, 1944, I, 262.

135. "Haemolytic disease of the newborn. The preponderance of homozygous Rh-positive fathers." G. L. Taylor and R. R. Race. *Brit. Med. Journ.*, February 26th, 1944, I, 288–9.

136. "Haemolytic disease of the newborn" (letter). L. G. Parsons. *Brit. Med. Journ.*, March 11th, 1944, I, 371.

NUTRITION

137. "The breast feeding of infants." *Min. Health Rept. Publ. Health and Med. Subj.*, 91, 1944.

138. "Calcium and phosphorus absorption in breast fed infants and its relationship to bone decalcification (rickets)." N. L. Wake. *Med. Journ. Austr.*, January 8th, 1944, XXXI, 27–30.

139. "The supply of unsweetened condensed milk for infants. Memorandum from the Commonwealth Controller of Emergency Supplies." *Med. Journ. Austr.*, January 15th, 1944, XXXI, 58.

140. "The use of evaporated milk without added sugar for the feeding of infants." H. McCulloch. *Amer. Journ. Dis. Childr.*, January 1944, LXVII, 52–5.

141. "Ueber deb Einfluss der B–Lactose auf die Darmflora des Säuglings." (Effect of B–lactose on the intestinal flora of infants.) A. Primnig and M. Turkus. *Zts. Kindersheilk.*, 1943, LXIII, 595–601. (*Nutr. Abstr. Rev.*, January 1944, XIII, 402.)

142. "Der Einfluss bestrahlter Milch auf die Rachitishäufigkeit unter Spätwinterkindern einer Grossstadt." (Effect of irradiated milk on the incidence of rickets in infants born in late winter in a city.) E. Mager. *Zts. Kinderheilk.*, 1943, LXIII, 631–41. (*Nutr. Abstr. Rev.*, January 1944, XIII, 462.)

143. "Milk intolerance, the cause of a nutritional entity. A clinical study." P. A. McLendon and D. S. Jaeger. *Southern Med. Journ.*, August 1943, XXXVI, 571–4. (*Bull. Hygiene*, January 1944, XIX, 2.)

144. "Subclinical vitamin deficiency. VI. Thiamine in skeletal muscle of infants and children." M. C. Hulse, N. Weissman, V. Rowland, R. Gross and J. W. Ferrebee. *Amer. Journ. Dis. Childr.*, January 1944, LXVII, 30–2.

WELFARE

145. "Use of current birth certificates in planning a maternal and child health program." W. C. Welling, M. L. Clifford and E. T. Tracy. *Amer. Journ. Publ. Health*, September 1943, XXXIII, 1115–23. (*Biol. Abstr.*, January 1944, XVIII, 145.)

146. "Conference on emergency maternity and infant welfare." Children's Bureau, U.S. Department of Labor. *Journ. Amer. Med. Assoc.*, December 25th, 1943, CXXIII, 1125–6.

147. "Emergency maternal and infant welfare." American Academy of Pediatrics. *Journ. Pediatr.*, January 1944, XXIV, 106–8.

148. "Emergency maternity and infant care program." Children's Bureau, U.S. Department of Labor. *Journ. Amer. Med. Assoc.*, January 22nd, 1944, CXXIV, 241–6.

MORTALITY

149. "Kindliche Mortalität in der Frauenklinik der Med. Akademie Düsseldorf." (Infant mortality in the Medical Academy, Düsseldorf.) W. Adams. *Ztschr. Geburtsh. Gynäk.*, 1942, CXXIV, 28. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 47.)

150. "Discussion on neonatal mortality." *Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 356–7.

151. "The lessons to be learned from a study of infant deaths." E. L. Potter. *Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 336–9.

152. "Immediate care of the newborn in relation to neonatal mortality." R. M. Tyson. *Journ. Amer. Med. Assoc.*, February 5th, 1944, CXXIV, 351–6.

153. "Prevention of neonatal disease and death." L. G. Parsons. *Lancet*, February 26th, 1944, I, 267–72.

154. "Poverty and child bearing." Editorial. *Lancet*, February 19th, 1944, I, 249–50.

155. "Nutrition and infant mortality." Debate in the House of Commons, March 8th, 1944. *Lancet*, March 18th, 1944, I, 387–8; *Brit. Med. Journ.*, March 25th, 1944, I, 441–2.

156. "Two enquiries into high infant mortality. I. Scotland. II. Northern Ireland." *Lancet*, February 19th, 1944, I, 255–6.

157. "Some aspects of the infant mortality problem in Belfast." J. Deeny and E. T. Murdock. *Ulster Med. Journ.*, November 1943.

158. "Statistical and social enquiry Society of Ireland. Infant mortality in the city of Belfast." J. Deeny and E. T. Murdock. Pamphlet, pp. 20, December 17th, 1943.

159. "Infant mortality in Scotland" (letters). *Brit. Med. Journ.*, 1944, I; February 5th, 193, S. F. Markham; February 26th, 300, D. Baird; February 26th, 301, M. S. M. McGregor; March 4th, 339, R. T. Rankin; March 11th, 372, M. S. M. McGregor.

160. "Death following circumcision." E. H. Barrett. *Med. Journ. Austr.*, December 11th, 1943, II, 490–1.

See also Ref. 58, 70.

MATERNAL WELFARE

161. "Maternity care for the wives of enlisted men." *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 881–3.

See also Ref. 145, 146, 147, 148.

MATERNAL MORTALITY

162. "Controllable factors in puerperal mortality in the borough of Brooklyn, City of New York, with an analysis of puerperal deaths of 1942." C. A. Gordon. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 884–9.

OBSTETRIC OPERATIONS

163. "Un caso de mioma uterino y embarazo. Cesarea e histerectomia al septimo mes." (A case of uterine myoma and pregnancy. Caesarean section and hysterectomy at the 7th month.) O. L. Ponte, R. D. Sisco and A. Rivero. *Rev. Obstet. y Ginec.* (Venezuela), 1943, III, 94–101.

164. "Twenty nine years of experience with Cesarean section." E. M. Lazard. *West. Journ. Surg.*, 1943, LI, 356. (*Int. Abstr. Surg.*, February 1944, LXXVIII, 146.)

165 "Cesarean section in Portland, Oregon during 1942." G. P. Lee. *West. Journ. Surg.*, 1943, LI, 330. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 44.)

166. "An evaluation of the transverse cervical Cesarean section. Report based on a study of 208 cases." G. W. Gustafson. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 841–8.

167. "Cesarea baja sementaria. Incision longitudinal o arciforme del segmento inferior." (Caesarean section. Longitudinal or curved incision of the lower segment.) R. G. Pastor. *Toko-Ginec. Pract.* (Madrid), December 1943, II, 318–31.

168. "Postmortem delivery of twins by forceps and manual manipulation." R. M. Allport. *Med. Journ. Austr.*, November 27th, 1943, II, 441.

See also Ref. 77, 78.

MISCELLANEOUS

169. "Problems in obstetrics. Perineal tears." M. Reddington. *Clin. Journ.*, March/April 1944, LXXIII, 51–4.

170. "Influence of industry on obstetrics and gynaecology. Discussion at the Association of Industrial Medical Officers." R. A. Brews *et al.* *Lancet*, March 18th, 1944, I, 373–4.

171. "The importance of focal infection in obstetrics." M. Solis-Cohen. *Surg., Gynecol. Obstet.*, January 1944, LXXVIII, 44–8.

172. "Rupture of the rectus abdominis muscle during pregnancy" (letter). J. B. Dawson. *Brit. Med. Journ.*, March 4th, 1944, I, 326.

GYNAECOLOGY

General

173. "Endocrinology in gynaecological practice." H. K. Pacey. *New Zealand Med. Journ.*, December 1943, XLII, Obstet. and Gynaecol. Section, 19–26.

174. "The hormones used in gynaecological practice." E. C. Dodds. *Practitioner*, March 1944, CLII, 129–34.

See also Ref. 28, 29, 170.

DISORDERS OF FUNCTION

Menstrual disorders

175. "Toxic effects in women exposed to industrial rubber solutions." J. L. Hamilton-Paterson and E. Browning. *Brit. Med. Journ.*, March 11th, 1944, I, 349–52.

176. "Menstrual disorders at puberty and adolescence." R. Sinha. *Calcutta Med. Journ.*, October 1943, XL, 395–404.

177. "Nutritional deficiency in the etiology of menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension. II. Further observations on treatment with the vitamin B complex." M. S. Biskind, G. R. Biskind and L. H. Biskind. *Surg., Gynecol. and Obstet.*, January 1944, LXXVIII, 49–57.

178. "Menstrual exercises." A. C. Dick. *Industr. Med.*, 1943, XII, 588. (*Int. Abstr. Surg.*, February 1944, LXXVIII, 142.)

179. "The psychosomatic treatment of functional dysmenorrhea by hypnosis. Preliminary report." W. S. Kroger and S. C. Freed. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 817–22.

180. "Oral hormonal treatment of functional amenorrhea." B. L. Cinberg. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 823–6.

181. "Anaphylactic shock after posterior pituitary extract injection (for menorrhagia)." E. Schleyer. *Brit. Med. Journ.*, February 19th, 1944, I, 255.

Menopause

182. "The aetiology and treatment of rheumatoid arthritis." L. S. P. Davidson. *Glasgow Med. Journ.*, January 1944. (Effect of the menopause on the time of onset of rheumatoid arthritis, p. 6.) Trans. Med.-Chir. Soc., 6–16.

Dyspareunia

183. "Dyspareunia." R. W. Johnstone. *Practitioner*, March 1944, CLII, 142–7.

Sterility

184. "Social and psychological factors affecting fertility. I. Differential fertility among 41,498 native-white couples in Indianapolis." P. K. Whelpton and C. V. Kiser. *Milbank Mem. Fund Quarterly*, 1943, XXI, 221–80. (*Nutr. Abstr. Rev.*, January 1944, XIII, 431.)

185. "Esterilidad de origen ovarico." (Sterility of ovarian origin.) M. G. Roca. *Med. Espan.*, December 1943, X, 772–6.

186. "Esterilidad de origen tubarico. Su tratamiento por insuflacion." (Sterility of tubal origin. Treatment by insufflation.) R. G. Pastor. *Med. Espan.*, December 1943, X, 825–31.

187. "Venous intravasation during utero-salpingography." E. R. Williams. *Brit. Journ. Radiol.*, January 1944, XVII, 13–17.

188. "Sterility." A. Bourne. *Practitioner*, March 1944, CLII, 135–41.

189. "Conception control. Report to the Council on Pharmacy and Chemistry of the American Medical Association." R. L. Dickinson. *Journ. Amer. Med. Assoc.*, December 18th, 1943, CXXIII, 1043–6.

ABNORMALITIES OF THE REPRODUCTIVE ORGANS

190. "Comentarios a proposito de las retrodesviaciones uterinas." (Retroflexion of the uterus.) L. A. Colomer. *Med. Espan.*, December 1943, X, 836–49.

191. "Double uterus, vagina and rectum." W. E. Ladd and T. C. Chisholm. *Amer. Journ. Dis. Childr.*, December 1943, LXVI, 629–34.

192. "Hermaphroditism." H. F. Bettinger. *Surg., Gynecol. and Obstet.*, January 1944, LXXVIII, 91–7.

INFECTIONS OF THE REPRODUCTIVE ORGANS

193. "The use of an acid jelly postoperatively after vaginal and cervical operations and in nonspecific infections of the vagina." K. J. Karnaky. *Texas Journ. Med.*, 1943, XXXIX, 178. (*Int. Abstr. Surg.*, February 1944, LXXVIII, 142.)

194. "Roentgen therapy of pelvic tuberculosis in the female." H. C. McIntosh. *Radiology*, January 1944, XLII, 48–55.

195. "Amebic infection of the vagina and uterus." E. M. Morse and S. P. Seaton. *Amer. Journ. Trop. Med.*, 1943, XXIII, 325–6. (*Biol. Abstr.*, December 1943, XVII, 2465.)

196. "Experimental basis for the chemotherapy of Trichomonas vaginalis infestations. I." G. Johnson and R. E. Trussell. *Proc. Soc. Exp. Biol. and Med.*, November 1943, LIV, 245–9.

197. "Vaginal ulceration and vitamin C deficiency" (letters). *Brit. Med. Journ.*, 1944, I. M. K. Lawlor and M. F. Richardson, February 19th, 254; F. B. Chisholm, March 4th, 338; M. K. Lawlor and M. F. Richardson, March 25th, 433.

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

198. "Androgen therapy in pelvic malignancy." C. T. Beecham. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 849–52.

199. "Post irradiation damage of the intestines following treatment of gynecological conditions." F. J. Lust. *Amer. Journ. Digest. Dis.*, January 1944, XI, 20–21.

200. "A case of retroperitoneal pelvic ganglioneuroma." S. G. Clayton. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 44–8.

201. "Two unusual cases of intraperitoneal bleeding giving rise to collapse." W. F. T. Haultain. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 38–41.

202. "Vaginal smears in uterine cancer." Editorial review. *Lancet*, March 11th, 1944, I, 346.

203. "Ueber das Vorkommen von Doppelcarcinomen am Uterus." (Occurrence of double cancer in the uterus.) B. Manstein. *Arch. Gynäk.*, 1942, CLXXIV, 153. (*Int. Abstr. Surg.*, February 1944, LXXVIII, 142.)

204. "Total pneumonectomy for metastatic uterine carcinoma." P. S. Brezina and G. E. Lindskog. *Journ. Thoracic Surg.*, December 1943, XII, 728–33.

205. "Carcinoma of the cervix. A study of 233 cases including 103 five-year cases with a survival rate of 33.9 per cent." J. R. Johnston. *Pennsylvania Med. Journ.*, 1943, XLVI, 1062–6. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 39.)

206. "La colposcopia el test de Schiller en el diagnostico precoz del cancer del cuello uterino." (Colposcopy and Schiller's test in the early diagnosis of cancer of the cervix.) M. A. Torrealba. *Rev. Obstet. y Ginec.* (Venezuela), 1943, III, 59–78.

207. "Nuestro metodo en el tratamiento del cancer del cuello uterino tipo III." (Our method of treating cancer of the cervix (type III).) V. Conill. *Toko-Ginec. Pract.* (Madrid), December 1943, II, 315–7.

208. "Carcinoma of the cervix; the Wertheim operation." J. V. Meigs. *Surg., Gynecol. and Obstet.*, February 1944, LXXVIII, 195–9.

209. "The diagnosis and treatment of carcinoma of the cervix." G. Hill. *Practitioner*, March 1944, CLII, 148–54.

210. "Further experiences in the management and treatment of carcinoma of the fundus of the uterus, with five-year end results in 75 patients." L. C. Scheffey, W. J. Thudium and D. M. Farrell. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 786–802.

211. "Hypertension arterielle et fibromyome uterin." (Arterial hypertension and uterine fibromyoma.) M. Loufti. *Rev. Med. Suisse Rom.*, 1943, 383. (*Int. Abstr. Surg.*, January 1944, LXXVIII, 39.)

212. "El enfermo tiene ascites. Cual es la causa? Fibrioma del utero?" (Is fibrioma of the uterus a cause of ascites?). S. M. Gomez. *Med. Espan.*, December 1943, X, 850–4.

213. "Chorionepithelioma after full term pregnancy and labour." C. Mukherjee. *Calcutta Med. Journ.*, December 1943, XL, 469–76: Editorial review, 485–8.

214. "Mesonephroma of the ovary." R. J. Jensik. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 810–16.

215. "Thecoma of the ovary associated with pleural effusion and ascites: Meigs syndrome." M. Perlmutter. *Ann. Int. Med.*, January 1944, XX, 132–40.

216. "Adrenal-like ovarian tumour associated with Cushing's syndrome (so-called masculinovoblastoma, luteoma, hypernephroma, adrenal cortical carcinoma of the ovary)." E. J. Kepler, M. B. Dockerty and J. T. Priestley. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 43–62.

217. "Adrenal rest tumor of the ovary." H. J. Greene and W. A. Lapp. *Amer. Journ. Obstet and Gynecol.*, January 1944, XLVII, 63–9.

218. "Ovarian tumours." S. Way. *Practitioner*, March 1944, CLII, 155–9.

219. "Endometriosis." W. W. Pascoe. *West. Journ. Surg.*, March 1943, LI, 123–6. (*Med. Journ. Austr.*, January 15th, 1944, XXXI, 54.)

GYNAECOLOGICAL OPERATIONS

220. "Ureteral injury during gynecological surgery." T. W. Adams. *West. Journ. Surg.*, 1943, LI, 305. (*Int. Abstr. Surg.*, February 1944, LXXVIII, 143.)

221. "The results of surgical castration in women under forty." W. Filler and N. Drezner. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 122–4.

222. "Treatment with penicillin after the failure of sulfa drugs in a case of vaginal plastic followed by blood stream infection." A. M. Hellman and E. F. Guilfoil. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 125–6.

223. "Artificial vagina" (letter). V. Gold. *Brit. Med. Journ.*, February 5th, 1944, I, 200.

224. "A unique constructive operation." V. Bonney and A. H. McIndoe. *Journ. Obstet. and Gynaecol. Brit. Emp.*, February 1944, LI, 24–9.

See also Ref. 24, 193, 208.

MISCELLANEOUS

225. "Findings in routine pelvic examinations on 1,998 women." E. L. Carey and C. J. Gaskill. *Amer. Journ. Obstet. and Gynecol.*, January 1944, XLVII, 111–17.

226. "Incarceration and strangulation of the cervix by a ring pessary." J. L. Goldrick and W. A. Lapp. *Amer. Journ. Obstet. and Gynecol.*, December 1943, XLVI, 877–8.

BOOKS

McGRAW, M. B. "Neuromuscular maturation of the human infant." Oxford: University Press, 1943, pp. 140.

PEEL, J. H. "Textbook of gynaecology (Forsdike)." London: Heinemann, 1943, pp. 440.

READ, G. D. "Revelation of childbirth." London: Heinemann, 1944.

RICCI, J. V. "The genealogy of gynaecology. History of the development of gynaecology throughout the ages, 2000 B.C. to 1800 A.D.: with excerpts from the many authors who have contributed to the various phases of the subject." Philadelphia: Blakiston, 1943.

ZABRISKIE, L. and EASTMAN, N. J. "Nurses' handbook of obstetrics." Philadelphia: Lippincott, 1943, pp. 714.